



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled, Parallel, 26 Week, Phase 3 Study of 2 Doses of an Alpha-7 Nicotinic Acetylcholine Receptor Agonist (EVP-6124) or Placebo as an Adjunctive Pro-cognitive Treatment in Schizophrenia Subjects on Chronic Stable Atypical Antipsychotic Therapy

Summary

EudraCT number	2012-003208-10
Trial protocol	DE ES PL
Global end of trial date	12 January 2016

Results information

Result version number	v1 (current)
This version publication date	28 January 2017
First version publication date	28 January 2017

Trial information

Trial identification

Sponsor protocol code	EVP-6124-015
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 076939

Notes:

Sponsors

Sponsor organisation name	Forum Pharmaceuticals Inc.
Sponsor organisation address	225 Second Avenue, Waltham, MA, United States, 02451
Public contact	SSU & Regulatory Lead, INC Research , valerie.desaedeleer@incresearch.com
Scientific contact	SSU & Regulatory Lead, INC Research , valerie.desaedeleer@incresearch.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	12 May 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are to assess the safety and the efficacy of 2 doses of once daily EVP-6124 tablets (1 and 2 mg) as an adjunctive pro-cognitive treatment, versus placebo, when added to chronic, stable, atypical antipsychotic therapy in subjects with schizophrenia. Safety will be determined by clinical and laboratory safety assessments. Efficacy will be determined by cognitive function as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS™) Consensus Cognitive Battery (MCCB™) Neurocognitive Composite Score, and by clinical function as measured by the interview-based Schizophrenia Cognition Rating Scale (SCoRS).

Protection of trial subjects:

Measures to minimize pain and discomfort secondary to phlebotomy were used on an as-needed basis. As there were no other invasive measures in this study, additional interventions were not needed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2012
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: 30
Country: Number of subjects enrolled	Spain: 53
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Argentina: 53
Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	Mexico: 40
Country: Number of subjects enrolled	Russian Federation: 57
Country: Number of subjects enrolled	Serbia: 24
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Ukraine: 56
Country: Number of subjects enrolled	United States: 349
Worldwide total number of subjects	753
EEA total number of subjects	106

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)	753
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects will be screened for eligibility within 28 days of entry into the single-blind placebo Run-in Period. On Day -14 subjects will be dispensed a 32-day supply of single-blind, placebo study medication.

Pre-assignment period milestones

Number of subjects started	1078 ^[1]
Number of subjects completed	753

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen Fails Prior to Run-In: 282
Reason: Number of subjects	Withdrawn Prior to Randomization: 43

Notes:

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

Justification: The worldwide number corresponds to the number of patients randomized (753) and not to the number of patients screened (1078).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	EVP-6124, 1 mg

Arm description:

Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).

Arm type	Experimental
Investigational medicinal product name	Encenicline
Investigational medicinal product code	EVP-6124
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects will be instructed to take 1 tablet of study medication once daily at the same time each day, preferably between 8 to 10 AM, with or without food, and with an adequate amount of water.

Arm title	EVP-6124, 2 mg
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Arm description:

Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).

Arm type	Experimental
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Investigational medicinal product name	Encenicline
Investigational medicinal product code	EVP-6124
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects will be instructed to take 1 tablet of study medication once daily at the same time each day, preferably between 8 to 10 AM, with or without food, and with an adequate amount of water.

Arm title	Placebo
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Arm description:

Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).

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

Dosage and administration details:

Subjects will be instructed to take 1 tablet of study medication once daily at the same time each day, preferably between 8 to 10 AM, with or without food, and with an adequate amount of water.

Number of subjects in period 1	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo
Started	252	248	253
Completed	199	185	200
Not completed	53	63	53
Consent withdrawn by subject	18	14	13
Physician decision	-	1	1
Medication prohibited by protocol	-	1	2
Adverse event, non-fatal	12	11	15
Administrative reasons	2	-	1
Other	3	5	1
Substance Abuse	8	6	3
Lost to follow-up	4	16	8
Protocol deviation	6	9	9

Baseline characteristics

Reporting groups

Reporting group title	EVP-6124, 1 mg
Reporting group description:	
Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).	
Reporting group title	EVP-6124, 2 mg
Reporting group description:	
Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).	
Reporting group title	Placebo
Reporting group description:	
Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).	

Reporting group values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo
Number of subjects	252	248	253
Age categorical			
Units: Subjects			
Adults (18-64 years)	252	248	253
Age continuous			
Units: years			
arithmetic mean	37	36.8	37.1
full range (min-max)	18 to 50	18 to 50	18 to 51
Gender categorical			
Units: Subjects			
Female	86	79	90
Male	166	169	163

Reporting group values	Total		
Number of subjects	753		
Age categorical			
Units: Subjects			
Adults (18-64 years)	753		
Age continuous			
Units: years			
arithmetic mean	-		
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	255		
Male	498		

End points

End points reporting groups

Reporting group title	EVP-6124, 1 mg
Reporting group description: Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).	
Reporting group title	EVP-6124, 2 mg
Reporting group description: Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).	
Reporting group title	Placebo
Reporting group description: Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).	

Primary: MATRICS Consensus Cognitive Battery (MCCB) Neurocognitive Composite T-Score with Imputation of missing components (Change from Baseline)

End point title	MATRICS Consensus Cognitive Battery (MCCB) Neurocognitive Composite T-Score with Imputation of missing components (Change from Baseline)
End point description:	
End point type	Primary
End point timeframe: Day -14 (training and practice) and testing on Days 1 (pre-dose), 28, 56, 84, and 182.	

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	238	246	
Units: n/a				
arithmetic mean (standard error)	3.9 (± 0.41)	4 (± 0.47)	3.2 (± 0.42)	

Statistical analyses

Statistical analysis title	Hochberg method adjustment
Comparison groups	EVP-6124, 1 mg v EVP-6124, 2 mg v Placebo
Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Hochberg method adjustment

Primary: Schizophrenia Cognition Rating Scale (SCoRS) Total Scores (Change from Baseline)

End point title	Schizophrenia Cognition Rating Scale (SCoRS) Total Scores (Change from Baseline)
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End point description:

End point type	Primary
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End point timeframe:

Day -14 (training and practice) and testing on Days 1 (pre-dose), 28, 56, 84, and 182.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	238	246	
Units: N/A				
arithmetic mean (full range (min-max))	-4.4 (-26 to 14)	-5 (-33 to 21)	-3.9 (-42 to 21)	

Statistical analyses

Statistical analysis title	Hochberg method adjustment
Comparison groups	EVP-6124, 1 mg v EVP-6124, 2 mg v Placebo
Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Hochberg method adjustment

Primary: MATRICS Consensus Cognitive Battery (MCCB) Neurocognitive Composite T-Score without Imputation of missing components (Change from Baseline)

End point title	MATRICS Consensus Cognitive Battery (MCCB) Neurocognitive Composite T-Score without Imputation of missing components (Change from Baseline)
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End point description:

End point type	Primary
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End point timeframe:

Day -14 (training and practice) and testing on Days 1 (pre-dose), 28, 56, 84, and 182.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	238	246	
Units: n/a				
arithmetic mean (full range (min-max))	4 (-10 to 35)	4.2 (-9 to 27)	3.1 (-17 to 21)	

Statistical analyses

Statistical analysis title	Hochberg method adjustment
Comparison groups	EVP-6124, 1 mg v EVP-6124, 2 mg v Placebo
Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Hochberg method adjustment

Primary: Summary of Treatment-Emergent Adverse Events (TEAE)

End point title	Summary of Treatment-Emergent Adverse Events (TEAE) ^[1]
End point description:	

End point type	Primary
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End point timeframe:

Any time after the subject signs the ICF through the follow-up period of the study (Day 182, 189, or ET, as applicable)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: Subjects with any TEAE	135	127	140	

Statistical analyses

No statistical analyses for this end point

Primary: Basophils (Change from baseline)

End point title	Basophils (Change from baseline) ^[2]
End point description:	

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: 10 ⁹ /L				
arithmetic mean (full range (min-max))	0 (-0.07 to 0.04)	0.001 (-0.06 to 0.08)	-0.003 (-0.11 to 0.04)	

Statistical analyses

No statistical analyses for this end point

Primary: Basophils/Leukocytes (Change from baseline)

End point title	Basophils/Leukocytes (Change from baseline) ^[3]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: percent				
arithmetic mean (full range (min-max))	0 (-1 to 1)	0.1 (-1 to 1)	-0.1 (-2 to 1)	

Statistical analyses

No statistical analyses for this end point

Primary: Eosinophils (Change from baseline)

End point title	Eosinophils (Change from baseline) ^[4]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: 10 ⁹ /L				
arithmetic mean (full range (min-max))	-0.003 (-0.55 to 0.64)	0.003 (-0.57 to 0.86)	-0.002 (-0.7 to 0.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Eosinophils/Leukocytes (Change from baseline)

End point title	Eosinophils/Leukocytes (Change from baseline) ^[5]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: percent				
arithmetic mean (full range (min-max))	-0.1 (-7 to 9)	0.1 (-9 to 10)	0 (-12 to 7)	

Statistical analyses

No statistical analyses for this end point

Primary: Erythrocytes (Change from baseline)

End point title	Erythrocytes (Change from baseline) ^[6]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: 10 ¹² /L				
arithmetic mean (full range (min-max))	0.037 (-0.56 to 1.57)	0.017 (-0.77 to 0.75)	-0.005 (-1.12 to 1.35)	

Statistical analyses

No statistical analyses for this end point

Primary: Hematocrit (Change from baseline)

End point title	Hematocrit (Change from baseline) ^[7]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: percent				
arithmetic mean (full range (min-max))	0.28 (-5.2 to 8)	0.25 (-8 to 8.3)	-0.12 (-9.7 to 10.2)	

Statistical analyses

No statistical analyses for this end point

Primary: Hemoglobin (Change from baseline)

End point title	Hemoglobin (Change from baseline) ^[8]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: g/dL				
arithmetic mean (full range (min-max))	0.01 (-1.9 to 3.2)	0 (-3.3 to 2.7)	-0.09 (-4.1 to 3.1)	

Statistical analyses

No statistical analyses for this end point

Primary: Leukocytes (Change from baseline)

End point title	Leukocytes (Change from baseline) ^[9]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: 10 ⁹ /L				
arithmetic mean (full range (min-max))	0.117 (-5.98 to 8)	0.018 (-5.8 to 6.6)	-0.046 (-14.92 to 8.4)	

Statistical analyses

No statistical analyses for this end point

Primary: Lymphocytes (Change from Baseline)

End point title	Lymphocytes (Change from Baseline) ^[10]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: 10 ⁹ /L				
arithmetic mean (full range (min-max))	0.016 (-1.99 to 3.19)	-0.002 (-1.89 to 2.27)	-0.016 (-2.27 to 1.77)	

Statistical analyses

No statistical analyses for this end point

Primary: Lymphocytes/Leukocytes (Change from baseline)

End point title	Lymphocytes/Leukocytes (Change from baseline) ^[11]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: percent				
arithmetic mean (full range (min-max))	-0.1 (-33 to 18)	-0.2 (-21 to 27)	-0.6 (-30 to 33)	

Statistical analyses

No statistical analyses for this end point

Primary: Monocytes (Change from baseline)

End point title	Monocytes (Change from baseline) ^[12]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: 10 ⁹ /L				
arithmetic mean (full range (min-max))	-0.002 (-0.43 to 0.78)	0.01 (-0.45 to 0.65)	-0.026 (-0.97 to 0.45)	

Statistical analyses

No statistical analyses for this end point

Primary: Monocytes/Leukocytes (Change from Baseline)

End point title	Monocytes/Leukocytes (Change from Baseline) ^[13]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: percent				
arithmetic mean (full range (min-max))	-0.1 (-6 to 7)	0.1 (-11 to 12)	-0.3 (-9 to 7)	

Statistical analyses

No statistical analyses for this end point

Primary: Neutrophils (Change from Baseline)

End point title Neutrophils (Change from Baseline)^[14]

End point description:

End point type Primary

End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: 10 ⁹ /L				
arithmetic mean (full range (min-max))	0.114 (-5.87 to 7.87)	-0.016 (-5.5 to 3.85)	0.006 (-14.06 to 8.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Neutrophils/Leukocytes (Change from Baseline)

End point title Neutrophils/Leukocytes (Change from Baseline)^[15]

End point description:

End point type Primary

End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: percent				
arithmetic mean (full range (min-max))	0.4 (-19 to 39)	-0.2 (-28 to 25)	0.9 (-37 to 36)	

Statistical analyses

No statistical analyses for this end point

Primary: Platelets (Change from Baseline)

End point title Platelets (Change from Baseline)^[16]

End point description:

End point type Primary

End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: 10 ⁹ /L				
arithmetic mean (full range (min-max))	3.6 (-94 to 112)	4.4 (-127 to 137)	0.9 (-183 to 112)	

Statistical analyses

No statistical analyses for this end point

Primary: Alanine Aminotransferase (Change from Baseline)

End point title Alanine Aminotransferase (Change from Baseline)^[17]

End point description:

End point type Primary

End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: IU/L				
arithmetic mean (full range (min-max))	0.9 (-43 to 52)	-2.3 (-146 to 48)	-0.6 (-47 to 53)	

Statistical analyses

No statistical analyses for this end point

Primary: Albumin (Change from Baseline)

End point title	Albumin (Change from Baseline) ^[18]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (± 2 days) or ET.

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: g/dL				
arithmetic mean (full range (min-max))	-0.01 (-0.7 to 0.6)	0.03 (-1 to 0.9)	-0.03 (-0.7 to 0.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Alkaline Phosphatase (Change from Baseline)

End point title	Alkaline Phosphatase (Change from Baseline) ^[19]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (± 2 days) or ET.

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: IU/L				
arithmetic mean (full range (min-max))	-0.6 (-39 to 61)	-0.7 (-69 to 36)	-0.5 (-41 to 48)	

Statistical analyses

No statistical analyses for this end point

Primary: Aspartate Aminotransferase (Change from Baseline)

End point title	Aspartate Aminotransferase (Change from Baseline) ^[20]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: IU/L				
arithmetic mean (full range (min-max))	1.5 (-30 to 116)	-2.9 (-273 to 33)	-1 (-94 to 64)	

Statistical analyses

No statistical analyses for this end point

Primary: Bicarbonate (Change from Baseline)

End point title	Bicarbonate (Change from Baseline) ^[21]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mEq/L				
arithmetic mean (full range (min-max))	-0.4 (-7 to 7)	-0.3 (-7 to 7)	-0.6 (-8 to 8)	

Statistical analyses

No statistical analyses for this end point

Primary: Bilirubin (Change from Baseline)

End point title Bilirubin (Change from Baseline)^[22]

End point description:

End point type Primary

End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mg/dL				
arithmetic mean (full range (min-max))	0 (-0.8 to 1.2)	0.01 (-0.6 to 1.3)	-0.03 (-0.9 to 1)	

Statistical analyses

No statistical analyses for this end point

Primary: Blood Urea Nitrogen (Change from Baseline)

End point title Blood Urea Nitrogen (Change from Baseline)^[23]

End point description:

End point type Primary

End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mg/dL				
arithmetic mean (full range (min-max))	0.1 (-9 to 10)	0 (-7 to 9)	-0.2 (-11 to 11)	

Statistical analyses

No statistical analyses for this end point

Primary: Calcium (Change from Baseline)

End point title	Calcium (Change from Baseline) ^[24]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mg/dL				
arithmetic mean (full range (min-max))	-0.04 (-1.3 to 0.8)	0.01 (-1 to 1.2)	-0.05 (-1.4 to 1)	

Statistical analyses

No statistical analyses for this end point

Primary: Chloride (Change from Baseline)

End point title	Chloride (Change from Baseline) ^[25]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mEq/L				
arithmetic mean (full range (min-max))	-0.4 (-7 to 5)	-0.7 (-8 to 6)	0.1 (-8 to 8)	

Statistical analyses

No statistical analyses for this end point

Primary: Creatine Phosphokinase (Change from Baseline)

End point title	Creatine Phosphokinase (Change from Baseline) ^[26]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: IU/L				
arithmetic mean (full range (min-max))	38.7 (-1954 to 4393)	-37.6 (-4953 to 1096)	-13.6 (-3903 to 4776)	

Statistical analyses

No statistical analyses for this end point

Primary: Creatinine (Change from Baseline)

End point title	Creatinine (Change from Baseline) ^[27]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mg/dL				
arithmetic mean (full range (min-max))	0.023 (-0.26 to 0.46)	0.008 (-0.34 to 0.75)	-0.004 (-0.62 to 0.37)	

Statistical analyses

No statistical analyses for this end point

Primary: Gamma Glutamyl Transferase (Change from Baseline)

End point title	Gamma Glutamyl Transferase (Change from Baseline) ^[28]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: IU/L				
arithmetic mean (full range (min-max))	-0.2 (-168 to 146)	-0.3 (-148 to 101)	0 (-462 to 297)	

Statistical analyses

No statistical analyses for this end point

Primary: Glucose (Change from Baseline)

End point title	Glucose (Change from Baseline) ^[29]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mg/dL				
arithmetic mean (full range (min-max))	1.3 (-138 to 222)	0.2 (-207 to 179)	2 (-97 to 138)	

Statistical analyses

No statistical analyses for this end point

Primary: Magnesium (Change from Baseline)

End point title	Magnesium (Change from Baseline) ^[30]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[30] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mg/dL				
arithmetic mean (full range (min-max))	-0.01 (-0.5 to 0.5)	-0.02 (-0.4 to 0.4)	0 (-0.6 to 1)	

Statistical analyses

No statistical analyses for this end point

Primary: Phosphate (Change from Baseline)

End point title	Phosphate (Change from Baseline) ^[31]			
End point description:				
End point type	Primary			
End point timeframe:				
The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (± 2 days) or ET.				
Notes:				
[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.				
Justification: Statistical tests were not performed on safety parameters.				
End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mg/dL				
arithmetic mean (full range (min-max))	-0.04 (-1.6 to 1.8)	-0.01 (-1.8 to 1.5)	-0.15 (-2.3 to 1.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Potassium (Change from Baseline)

End point title	Potassium (Change from Baseline) ^[32]			
End point description:				
End point type	Primary			
End point timeframe:				
The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (± 2 days) or ET.				
Notes:				
[32] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.				
Justification: Statistical tests were not performed on safety parameters.				
End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mEq/L				
arithmetic mean (full range (min-max))	0 (-1.1 to 1.6)	0.05 (-2.2 to 1.1)	0 (-1.3 to 1)	

Statistical analyses

No statistical analyses for this end point

Primary: Protein (Change from Baseline)

End point title	Protein (Change from Baseline) ^[33]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: g/dL				
arithmetic mean (full range (min-max))	-0.04 (-1.2 to 1)	0 (-1.7 to 1.6)	-0.06 (-1 to 1.3)	

Statistical analyses

No statistical analyses for this end point

Primary: Sodium (Change from Baseline)

End point title	Sodium (Change from Baseline) ^[34]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[34] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mEq/L				
arithmetic mean (full range (min-max))	-0.1 (-11 to 7)	-0.2 (-8 to 8)	0 (-10 to 7)	

Statistical analyses

No statistical analyses for this end point

Primary: Urate (Change from Baseline)

End point title	Urate (Change from Baseline) ^[35]
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End point description:

End point type	Primary
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End point timeframe:

The non-fasting laboratory tests will be performed at the screening visit and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[35] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mg/dL				
arithmetic mean (full range (min-max))	0.05 (-3.3 to 3)	0.01 (-2.2 to 3.8)	-0.16 (-3.6 to 2.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Systolic Blood Pressure (Change from Baseline)

End point title	Systolic Blood Pressure (Change from Baseline) ^[36]
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End point description:

End point type	Primary
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End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[36] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mmHg				
arithmetic mean (full range (min-max))	-0.2 (-40 to 33)	-0.2 (-26 to 32)	0.3 (-42 to 42)	

Statistical analyses

No statistical analyses for this end point

Primary: Diastolic Blood Pressure (Change from Baseline)

End point title	Diastolic Blood Pressure (Change from Baseline) ^[37]
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End point description:

End point type	Primary
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End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: mmHg				
arithmetic mean (full range (min-max))	0.2 (-27 to 23)	-0.8 (-25 to 26)	0.1 (-25 to 25)	

Statistical analyses

No statistical analyses for this end point

Primary: Pulse Rate (Change from Baseline)

End point title	Pulse Rate (Change from Baseline) ^[38]
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End point description:

End point type	Primary
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End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[38] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: BEATS/MIN				
arithmetic mean (full range (min-max))	-0.7 (-36 to 30)	-0.3 (-30 to 26)	1.4 (-25 to 40)	

Statistical analyses

No statistical analyses for this end point

Primary: Respiratory Rate (Change from Baseline)

End point title Respiratory Rate (Change from Baseline)^[39]

End point description:

End point type Primary

End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[39] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	252	
Units: BREATHS/MIN				
arithmetic mean (full range (min-max))	-0.1 (-12 to 8)	0 (-7 to 10)	0 (-8 to 6)	

Statistical analyses

No statistical analyses for this end point

Primary: Temperature (Change from Baseline)

End point title Temperature (Change from Baseline)^[40]

End point description:

End point type Primary

End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[40] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: celsius				
arithmetic mean (full range (min-max))	0.02 (-1.6 to 1.5)	0.01 (-1 to 1.1)	-0.05 (-1.7 to 1)	

Statistical analyses

No statistical analyses for this end point

Primary: Weight (Change from Baseline)

End point title	Weight (Change from Baseline) ^[41]
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End point description:

End point type	Primary
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End point timeframe:

Screening visit, Day 1 (pre-dose) and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[41] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: kg				
arithmetic mean (full range (min-max))	1.01 (-14 to 14.9)	1 (-17.7 to 17.3)	0.07 (-15.3 to 9.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Heart Rate (Change from Baseline)

End point title	Heart Rate (Change from Baseline) ^[42]
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End point description:

End point type	Primary
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End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[42] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: BEATS/MIN				
arithmetic mean (full range (min-max))	-0.4 (-38 to 32)	0.9 (-30 to 28)	1 (-31 to 45)	

Statistical analyses

No statistical analyses for this end point

Primary: QT Duration (Change from Baseline)

End point title QT Duration (Change from Baseline)^[43]

End point description:

End point type Primary

End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[43] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: msec				
arithmetic mean (full range (min-max))	-0.4 (-67 to 82)	0.1 (-54 to 82)	-2.1 (-105 to 75)	

Statistical analyses

No statistical analyses for this end point

Primary: QTcB - Bazett's Correction Formula (Change from baseline)

End point title QTcB - Bazett's Correction Formula (Change from baseline)^[44]

End point description:

End point type Primary

End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[44] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: msec				
arithmetic mean (full range (min-max))	-1.2 (-59 to 73)	2.5 (-50 to 65)	0.8 (-79 to 50)	

Statistical analyses

No statistical analyses for this end point

Primary: QTcF - Fridericia's Correction Formula (Change from baseline)

End point title	QTcF - Fridericia's Correction Formula (Change from
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End point description:

End point type	Primary
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End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[45] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: msec				
arithmetic mean (full range (min-max))	-0.9 (-50 to 53)	1.6 (-41 to 50)	-0.3 (-68 to 38)	

Statistical analyses

No statistical analyses for this end point

Primary: QRS Duration (Change from Baseline)

End point title	QRS Duration (Change from Baseline) ^[46]
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End point description:

End point type	Primary
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End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[46] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: msec				
arithmetic mean (full range (min-max))	-1.1 (-21 to 16)	-0.6 (-22 to 19)	-0.6 (-25 to 30)	

Statistical analyses

No statistical analyses for this end point

Primary: PR Duration (Change from Baseline)

End point title	PR Duration (Change from Baseline) ^[47]
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End point description:

End point type	Primary
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End point timeframe:

Screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET.

Notes:

[47] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: msec				
arithmetic mean (full range (min-max))	2.8 (-46 to 58)	-0.8 (-32 to 44)	-0.5 (-29 to 41)	

Statistical analyses

No statistical analyses for this end point

Primary: Calgary Depression Severity in Schizophrenia (CDSS) (Day 182)

End point title	Calgary Depression Severity in Schizophrenia (CDSS) (Day 182) ^[48]
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End point description:

End point type	Primary
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End point timeframe:

Screening visit, Day 1 (Pre-dose), Day 182 and on ET.

Notes:

[48] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: n/a				
arithmetic mean (full range (min-max))	1.3 (0 to 9)	1.2 (0 to 13)	1.1 (0 to 9)	

Statistical analyses

No statistical analyses for this end point

Primary: Columbia Suicide-Severity Rating Scale (C-SSRS) (Day 182)

End point title	Columbia Suicide-Severity Rating Scale (C-SSRS) (Day 182) ^[49]
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End point description:

End point type	Primary
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End point timeframe:

Screening, Days 1 (pre-dose), 14 (telephone call), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or early termination.

Notes:

[49] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: Subjects with suicidal behavior/ideation	5	1	4	

Statistical analyses

No statistical analyses for this end point

Primary: Simpson-Angus Total Scores (SAS) (Change from baseline)

End point title	Simpson-Angus Total Scores (SAS) (Change from baseline) ^[50]
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End point description:

End point type	Primary
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End point timeframe:

Screening and on Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (\pm 2 days) or ET

Notes:

[50] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: n/a				
arithmetic mean (full range (min-max))	-0.2 (-9 to 4)	0 (-6 to 4)	-0.1 (-4 to 4)	

Statistical analyses

No statistical analyses for this end point

Primary: Positive and Negative Syndrome Scale (PANSS) Positive Symptom Scores (Change from baseline)

End point title	Positive and Negative Syndrome Scale (PANSS) Positive Symptom Scores (Change from baseline) ^[51]
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End point description:

End point type	Primary
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End point timeframe:

Days -14, 1 (pre-dose), and 28, 56, 84, 112, 140, and 182.

Notes:

[51] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical tests were not performed on safety parameters.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	248	253	
Units: n/a				
arithmetic mean (full range (min-max))	-1.5 (-9 to 13)	-1.2 (-9 to 8)	-1 (-7 to 9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Positive and Negative Syndrome Scale (PANSS) Negative Symptom Factor (Marder Factor) (Change from Baseline)

End point title	Positive and Negative Syndrome Scale (PANSS) Negative Symptom Factor (Marder Factor) (Change from Baseline)
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End point description:

End point type	Secondary
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End point timeframe:

Days -14, 1 (pre-dose), and 28, 56, 84, 112, 140, and 182.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	238	246	
Units: n/a				
arithmetic mean (full range (min-max))	-2.6 (-12 to 8)	-2.1 (-13 to 8)	-1.8 (-14 to 9)	

Statistical analyses

Statistical analysis title	Hochberg method adjustment
Comparison groups	EVP-6124, 1 mg v EVP-6124, 2 mg v Placebo
Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Hochberg method adjustment

Secondary: MATRICS Consensus Cognitive Battery (MCCB) Overall Composite T-Scores with Imputation of missing components (Change from Baseline)

End point title	MATRICS Consensus Cognitive Battery (MCCB) Overall Composite T-Scores with Imputation of missing components (Change from Baseline)
End point description:	
End point type	Secondary
End point timeframe:	Day -14 (training and practice) and testing on Days 1 (pre-dose), 28, 56, 84, and 182.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	238	246	
Units: n/a				
arithmetic mean (standard error)	3.6 (± 0.41)	3.5 (± 0.49)	2.8 (± 0.45)	

Statistical analyses

No statistical analyses for this end point

Secondary: MATRICS Consensus Cognitive Battery (MCCB) Overall Composite T-Scores without Imputation of missing components (Change from Baseline)

End point title	MATRICS Consensus Cognitive Battery (MCCB) Overall Composite T-Scores without Imputation of missing components
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(Change from Baseline)

End point description:

End point type Secondary

End point timeframe:

Day -14 (training and practice) and testing on Days 1 (pre-dose), 28, 56, 84, and 182.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	238	246	
Units: n/a				
arithmetic mean (full range (min-max))	3.7 (-14 to 33)	3.7 (-10 to 29)	2.7 (-18 to 22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Schizophrenia Cognition Rating Scale (SCoRS) Global rating (Change from Baseline)

End point title Schizophrenia Cognition Rating Scale (SCoRS) Global rating (Change from Baseline)

End point description:

End point type Secondary

End point timeframe:

Day -14 (training and practice) and testing on Days 1 (pre-dose), 28, 56, 84, and 182.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	238	246	
Units: n/a				
arithmetic mean (full range (min-max))	-0.8 (-5 to 2)	-1 (-5 to 3)	-0.9 (-6 to 3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Positive and Negative Syndrome Scale (PANSS) Negative Symptom Scores (Change from baseline)

End point title Positive and Negative Syndrome Scale (PANSS) Negative Symptom Scores (Change from baseline)

End point description:

End point type	Secondary
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End point timeframe:

Days -14, 1 (pre-dose), and 28, 56, 84, 112, 140, and 182.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	238	246	
Units: n/a				
arithmetic mean (full range (min-max))	-2.5 (-13 to 7)	-1.7 (-11 to 9)	-1.6 (-15 to 10)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression – Severity scale (CGI-S) (Day 182)

End point title	Clinical Global Impression – Severity scale (CGI-S) (Day 182)
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End point description:

End point type	Secondary
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End point timeframe:

Days 1 (pre-dose, baseline), and 28, 56, 84, 112, 140, and 182.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	238	246	
Units: n/a				
arithmetic mean (full range (min-max))	3.2 (1 to 5)	3.2 (2 to 5)	3.3 (1 to 5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression – Change scale (CGI-C) (Day 182)

End point title	Clinical Global Impression – Change scale (CGI-C) (Day 182)
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End point description:

End point type	Secondary
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End point timeframe:

Days 28, 56, 84, 112, 140, and 182

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	238	246	
Units: n/a				
arithmetic mean (full range (min-max))	3.1 (1 to 5)	3.1 (1 to 6)	3.2 (1 to 5)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events observed at any time after the subject signs the informed consent through the follow-up period of the study (Day 182, 189, or ET, as applicable) are to be recorded.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	EVP-6124, 1 mg
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Reporting group description:

Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).

Reporting group title	EVP-6124, 2 mg
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Reporting group description:

Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).

Reporting group title	Placebo
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Reporting group description:

Eligible subjects will be randomized in a 1:1:1 allocation to 1 of 3 double-blind treatment groups: once daily EVP-6124 tablets (1 or 2 mg) or placebo for 26 weeks (Days 1 to 182).

Serious adverse events	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 252 (2.38%)	3 / 248 (1.21%)	7 / 253 (2.77%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Alcohol poisoning			

subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Multiple fractures			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychiatric decompensation			
subjects affected / exposed	3 / 252 (1.19%)	2 / 248 (0.81%)	3 / 253 (1.19%)
occurrences causally related to treatment / all	1 / 6	0 / 3	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 252 (0.00%)	2 / 248 (0.81%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			

subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed mood			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, auditory			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Tuberculosis			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	EVP-6124, 1 mg	EVP-6124, 2 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	135 / 252 (53.57%)	127 / 248 (51.21%)	140 / 253 (55.34%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Thyroid neoplasm			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 135	4 / 248 (1.61%) 127	2 / 253 (0.79%) 140
Hot flush subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	6 / 252 (2.38%) 135	5 / 248 (2.02%) 127	5 / 253 (1.98%) 140
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	2 / 253 (0.79%) 140
Pain subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	1 / 248 (0.40%) 127	1 / 253 (0.40%) 140
Pyrexia subjects affected / exposed occurrences (all)	3 / 252 (1.19%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Chest pain subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	2 / 248 (0.81%) 127	0 / 253 (0.00%) 140
Cyst subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Discomfort subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Feeling abnormal subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Feeling hot subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Peripheral swelling			

subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Temperature intolerance subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	2 / 253 (0.79%) 140
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Social circumstances Substance use subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	1 / 253 (0.40%) 140
Ovarian cyst subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	1 / 253 (0.40%) 140
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Breast calcifications subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Breast disorder subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Breast hyperplasia subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Breast swelling			

subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Dysmenorrhoea			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Erectile dysfunction			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Gynaecomastia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Lactation disorder			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Menstrual disorder			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Nipple pain			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Premenstrual pain			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Sexual dysfunction			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 252 (1.19%)	3 / 248 (1.21%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Oropharyngeal pain			
subjects affected / exposed	2 / 252 (0.79%)	4 / 248 (1.61%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Epistaxis			

subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Nasal congestion			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Rhinorrhoea			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	3 / 253 (1.19%)
occurrences (all)	135	127	140
Allergic sinusitis			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Asthma			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Bradypnoea			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Bronchitis chronic			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Catarrh			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Dyspnoea			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Productive cough			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Respiratory disorder			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Rhinitis allergic			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Snoring			

subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Upper respiratory tract congestion subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Wheezing subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	12 / 252 (4.76%) 135	9 / 248 (3.63%) 127	10 / 253 (3.95%) 140
Anxiety subjects affected / exposed occurrences (all)	8 / 252 (3.17%) 135	5 / 248 (2.02%) 127	12 / 253 (4.74%) 140
Psychiatric decompensation subjects affected / exposed occurrences (all)	6 / 252 (2.38%) 135	7 / 248 (2.82%) 127	8 / 253 (3.16%) 140
Suicidal ideation subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 135	3 / 248 (1.21%) 127	1 / 253 (0.40%) 140
Hallucination, auditory subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 135	1 / 248 (0.40%) 127	1 / 253 (0.40%) 140
Irritability subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	2 / 253 (0.79%) 140
Psychotic disorder subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Depressed mood subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Psychomotor retardation subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140

Thinking abnormal subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	2 / 253 (0.79%) 140
Agitation subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Bruxism subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Confusional state subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Delusion subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 124	0 / 253 (0.00%) 140
Depression subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Hallucination subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Initial insomnia subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Libido decreased subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Middle insomnia subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Panic attack subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Paranoia subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140

Restlessness			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Sleep disorder			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Somnambulism			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Suicide attempt			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 252 (1.98%)	12 / 248 (4.84%)	16 / 253 (6.32%)
occurrences (all)	135	123	140
Weight increased			
subjects affected / exposed	12 / 252 (4.76%)	11 / 248 (4.44%)	7 / 253 (2.77%)
occurrences (all)	135	127	140
Alanine aminotransferase increased			
subjects affected / exposed	4 / 252 (1.59%)	1 / 248 (0.40%)	4 / 253 (1.58%)
occurrences (all)	135	127	140
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 252 (1.98%)	0 / 248 (0.00%)	4 / 253 (1.58%)
occurrences (all)	135	127	140
Weight decreased			
subjects affected / exposed	0 / 252 (0.00%)	6 / 248 (2.42%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Blood glucose increased			
subjects affected / exposed	0 / 252 (0.00%)	6 / 248 (2.42%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Blood uric acid increased			
subjects affected / exposed	3 / 252 (1.19%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Blood pressure increased			

subjects affected / exposed	0 / 252 (0.00%)	2 / 248 (0.81%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Neutrophil count increased			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	3 / 253 (1.19%)
occurrences (all)	135	127	140
White blood cell count increased			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	3 / 253 (1.19%)
occurrences (all)	135	127	140
Blood bilirubin increased			
subjects affected / exposed	2 / 252 (0.79%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Blood urea increased			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Urine leukocyte esterase positive			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
White blood cell count decreased			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Aspartate aminotransferase abnormal			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Blood alcohol increased			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Blood cholesterol increased			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140

Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Blood glucose decreased subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Blood potassium decreased subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Blood pressure diastolic decreased subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Blood prolactin increased subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Blood urine present subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Gamma-glutamyltransferase abnormal subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Glucose urine present subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Nitrite urine present subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Platelet count increased			

subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Protein total increased			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Protein urine present			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Red blood cell count increased			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Urinary casts			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Urine ketone body present			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 252 (2.38%)	2 / 248 (0.81%)	5 / 253 (1.98%)
occurrences (all)	135	127	140
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	4 / 253 (1.58%)
occurrences (all)	135	127	140
Thermal burn			
subjects affected / exposed	2 / 252 (0.79%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Ligament sprain			
subjects affected / exposed	0 / 252 (0.00%)	2 / 248 (0.81%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Limb injury			
subjects affected / exposed	2 / 252 (0.79%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Toxicity to various agents			

subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Accidental overdose			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Alcohol poisoning			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Excoriation			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Eye contusion			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Multiple fractures			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Muscle injury			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Muscle strain			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Radius fracture			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Road traffic accident			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Scar			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Skin abrasion			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Soft tissue injury			

subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Sunburn			
subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Arthropod bite			
subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Cardiac disorders			
Defect conduction intraventricular subjects affected / exposed occurrences (all)	3 / 252 (1.19%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Atrioventricular block first degree subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Atrioventricular block second degree subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Bradycardia subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Bundle branch block left subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Sinus bradycardia subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Tachycardia subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Nervous system disorders			
Headache			

subjects affected / exposed	24 / 252 (9.52%)	16 / 248 (6.45%)	15 / 253 (5.93%)
occurrences (all)	135	127	140
Somnolence			
subjects affected / exposed	2 / 252 (0.79%)	2 / 248 (0.81%)	6 / 253 (2.37%)
occurrences (all)	135	127	140
Tremor			
subjects affected / exposed	4 / 252 (1.59%)	2 / 248 (0.81%)	3 / 253 (1.19%)
occurrences (all)	135	127	140
Dizziness			
subjects affected / exposed	4 / 252 (1.59%)	2 / 248 (0.81%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Disturbance in attention			
subjects affected / exposed	2 / 252 (0.79%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Sedation			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	3 / 253 (1.19%)
occurrences (all)	135	127	140
Akathisia			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Extrapyramidal disorder			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Hypersomnia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Hypoaesthesia			
subjects affected / exposed	0 / 252 (0.00%)	2 / 248 (0.81%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Dysgeusia			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Dyskinesia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Extensor plantar response			

subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Glabellar reflex abnormal			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Hyporeflexia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Hypotonia			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Migraine			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Paraesthesia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Radial nerve compression			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Restless legs syndrome			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Sinus headache			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Stupor			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Tension headache			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
VIIth nerve paralysis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Lymphadenopathy			
subjects affected / exposed	2 / 252 (0.79%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Eosinophilia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Leukocytosis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Neutrophilia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Vertigo			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Vision blurred			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Blepharospasm			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Eye irritation			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	14 / 252 (5.56%)	19 / 248 (7.66%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Diarrhoea			
subjects affected / exposed	3 / 252 (1.19%)	7 / 248 (2.82%)	5 / 253 (1.98%)
occurrences (all)	135	127	140
Nausea			
subjects affected / exposed	4 / 252 (1.59%)	4 / 248 (1.61%)	4 / 253 (1.58%)
occurrences (all)	135	127	140
Toothache			
subjects affected / exposed	5 / 252 (1.98%)	3 / 248 (1.21%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Dyspepsia			
subjects affected / exposed	3 / 252 (1.19%)	3 / 248 (1.21%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Abdominal pain			
subjects affected / exposed	1 / 252 (0.40%)	2 / 248 (0.81%)	3 / 253 (1.19%)
occurrences (all)	135	127	140
Abdominal pain upper			
subjects affected / exposed	2 / 252 (0.79%)	2 / 248 (0.81%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Vomiting			
subjects affected / exposed	2 / 252 (0.79%)	1 / 248 (0.40%)	3 / 253 (1.19%)
occurrences (all)	135	127	140
Abdominal discomfort			
subjects affected / exposed	1 / 252 (0.40%)	2 / 248 (0.81%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Faeces hard			
subjects affected / exposed	1 / 252 (0.40%)	2 / 248 (0.81%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 252 (0.79%)	1 / 248 (0.40%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Dry mouth			
subjects affected / exposed	2 / 252 (0.79%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140

Gastritis			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Haematochezia			
subjects affected / exposed	0 / 252 (0.00%)	2 / 248 (0.81%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Rectal haemorrhage			
subjects affected / exposed	2 / 252 (0.79%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Abdominal distension			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Anal fissure			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Abdominal pain lower			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Aphthous stomatitis			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Chronic gastritis			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Dental caries			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Flatulence			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Gingival pain			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Gingival swelling			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140

Haemorrhoidal haemorrhage subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Haemorrhoids subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Irritable bowel syndrome subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Oesophagitis subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Painful defaecation subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	1 / 248 (0.40%) 127	0 / 253 (0.00%) 140
Salivary gland calculus subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Stomatitis subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Rash subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	2 / 253 (0.79%) 140
Alopecia subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 135	0 / 248 (0.00%) 127	0 / 253 (0.00%) 140
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 135	0 / 248 (0.00%) 127	1 / 253 (0.40%) 140
Eczema asteatotic			

subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Erythema			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Hyperhidrosis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Nail bed disorder			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Nail disorder			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Pain of skin			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Petechiae			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Photosensitivity reaction			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Pruritus			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Psoriasis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Skin disorder			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Skin fissures			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Skin hypopigmentation			

subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Skin lesion			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Skin mass			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Skin ulcer			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Urticaria			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 252 (0.00%)	3 / 248 (1.21%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Dysuria			
subjects affected / exposed	2 / 252 (0.79%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Proteinuria			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Glycosuria			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Ketonuria			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Nephrolithiasis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Endocrine disorders			
Hyperprolactinaemia			

subjects affected / exposed	2 / 252 (0.79%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 252 (2.38%)	5 / 248 (2.02%)	10 / 253 (3.95%)
occurrences (all)	135	127	140
Arthralgia			
subjects affected / exposed	1 / 252 (0.40%)	2 / 248 (0.81%)	4 / 253 (1.58%)
occurrences (all)	135	127	140
Pain in extremity			
subjects affected / exposed	1 / 252 (0.40%)	5 / 248 (2.02%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Musculoskeletal pain			
subjects affected / exposed	1 / 252 (0.40%)	2 / 248 (0.81%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Myalgia			
subjects affected / exposed	1 / 252 (0.40%)	2 / 248 (0.81%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Muscle spasms			
subjects affected / exposed	2 / 252 (0.79%)	0 / 248 (0.00%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Neck pain			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Arthritis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Muscle rigidity			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Muscle twitching			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Muscular weakness			

subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Musculoskeletal chest pain			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Nuchal rigidity			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Osteitis			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Torticollis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 252 (4.37%)	17 / 248 (6.85%)	14 / 253 (5.53%)
occurrences (all)	135	127	140
Bronchitis			
subjects affected / exposed	4 / 252 (1.59%)	2 / 248 (0.81%)	4 / 253 (1.58%)
occurrences (all)	135	127	140
Influenza			
subjects affected / exposed	3 / 252 (1.19%)	4 / 248 (1.61%)	3 / 253 (1.19%)
occurrences (all)	135	127	140
Upper respiratory tract infection			
subjects affected / exposed	2 / 252 (0.79%)	4 / 248 (1.61%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Pharyngitis			
subjects affected / exposed	4 / 252 (1.59%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Ear infection			
subjects affected / exposed	2 / 252 (0.79%)	1 / 248 (0.40%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Gastroenteritis			
subjects affected / exposed	2 / 252 (0.79%)	0 / 248 (0.00%)	2 / 253 (0.79%)
occurrences (all)	135	127	140

Conjunctivitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Respiratory tract infection			
subjects affected / exposed	1 / 252 (0.40%)	2 / 248 (0.81%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Tooth infection			
subjects affected / exposed	2 / 252 (0.79%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Urinary tract infection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Cystitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Gastroenteritis viral			
subjects affected / exposed	2 / 252 (0.79%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Gingivitis			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Hordeolum			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Respiratory tract infection viral			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Sinusitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Subcutaneous abscess			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Tonsillitis			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140

Viral upper respiratory tract infection			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Acarodermatitis			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Eye infection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Fungal infection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Genital infection fungal			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Herpes simplex			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Localised infection			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Pharyngitis streptococcal			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Pneumonia			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Pulpitis dental			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Rhinitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Tinea pedis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140

Tooth abscess			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Tuberculosis			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Varicella			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Viral infection			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Viral rhinitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Wound infection			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 252 (0.40%)	2 / 248 (0.81%)	2 / 253 (0.79%)
occurrences (all)	135	127	140
Hyperglycaemia			
subjects affected / exposed	3 / 252 (1.19%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Diabetes mellitus			
subjects affected / exposed	1 / 252 (0.40%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Dehydration			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Dyslipidaemia			

subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Gout			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Hypercholesterolaemia			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Hyperlipidaemia			
subjects affected / exposed	0 / 252 (0.00%)	0 / 248 (0.00%)	1 / 253 (0.40%)
occurrences (all)	135	127	140
Hypoglycaemia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 248 (0.40%)	0 / 253 (0.00%)
occurrences (all)	135	127	140
Obesity			
subjects affected / exposed	1 / 252 (0.40%)	0 / 248 (0.00%)	0 / 253 (0.00%)
occurrences (all)	135	127	140

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2013	Protocol Amendment 1
08 July 2013	Protocol Amendment 2
05 December 2013	Protocol Amendment 2.1
26 August 2014	Protocol Amendment 2.2
30 September 2015	Protocol Amendment 3
01 October 2015	Protocol Amendment 3.1

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported