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	2012-003209-92
Trial protocol	GB IT PL
Global end of trial date	14 December 2015

Results information

Result version number	v2 (current)
This version publication date	28 January 2017
First version publication date	31 December 2016
Version creation reason	• Correction of full data set The endpoint "Columbia Suicide-Severity Rating Scale (C-SSRS) (Day 182)" should be listed as a primary endpoint.

Trial information

Trial identification

Sponsor protocol code	EVP-6124-016

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	14 December 2015
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	31 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: 19
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Argentina: 26
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Colombia: 51
Country: Number of subjects enrolled	Mexico: 19
Country: Number of subjects enrolled	Romania: 43
Country: Number of subjects enrolled	Russian Federation: 73
Country: Number of subjects enrolled	Ukraine: 147
Country: Number of subjects enrolled	United States: 354
Worldwide total number of subjects	766
EEA total number of subjects	93

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)	766
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	1146[1]
Intermediate milestone: Number of subjects	Entered Run-In: 818
Number of subjects completed	766

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen Fails Prior to Run-In: 329
Reason: Number of subjects	Withdrawn Prior to Randomization: 51

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 (766) and not to the number of patients screened (1146).

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

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	Placebo

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	258	254	254
Completed	205	193	200
Not completed	53	61	54
Physician decision	1	1	1
Consent withdrawn by subject	19	27	19
Medication prohibited by protocol	1	1	-
Adverse event, non-fatal	14	9	13
Other	1	2	2
Substance Abuse	6	7	3
Lost to follow-up	8	7	13
Protocol deviation	3	7	3

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	258	254	254
Age categorical Units: Subjects			
Adults (18-64 years)	258	254	254
Age continuous Units: years			
arithmetic mean	36.6	36.6	35.9
full range (min-max)	18 to 50	18 to 50	19 to 50
Gender categorical Units: Subjects			
Female	99	74	100
Male	159	180	154

Reporting group values	Total		
Number of subjects	766		
Age categorical Units: Subjects			
Adults (18-64 years)	766		
Age continuous Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	273		
Male	493		

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 Cognition Battery (MCCB) Neurocognitive Composite T-Scores with imputation of missing components (Change from baseline)

End point title	MATRICS Consensus Cognition Battery (MCCB) Neurocognitive Composite T-Scores 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	255	251	250	
Units: n/a				
arithmetic mean (standard error)	3.4 (± 0.42)	3.4 (± 0.46)	3 (± 0.41)	

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	756
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)

End point description:

End point type	Primary

End point timeframe:

On 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	255	251	250	
Units: n/a				
arithmetic mean (full range (min-max))	-3.3 (-21 to 30)	-3.7 (-23 to 27)	-3.4 (-28 to 17)	

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	756
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Hochberg method adjustment

Primary: MATRICS Consensus Cognition Battery (MCCB) Neurocognitive Composite T-scores without imputation of missing components (Change from baseline)

End point title	MATRICS Consensus Cognition Battery (MCCB) Neurocognitive Composite T-scores without imputation of missing components (Change from baseline)

End point description:

End point type	Primary

End point timeframe:

On 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	255	251	250	
Units: n/a				
arithmetic mean (full range (min-max))	3.5 (-15 to 20)	3.7 (-12 to 23)	2.9 (-14 to 19)	

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	756
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

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	258	254	254	
Units: Subjects with any TEAE	127	127	148	

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

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:

[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	258	254	254	
Units: 10^9/L				
arithmetic mean (full range (min-max))	0.003 (-0.06 to 0.12)	0 (-0.11 to 0.07)	-0.002 (-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]

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:

[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	258	254	254	
Units: percent				
arithmetic mean (full range (min-max))	0 (-1 to 1)	0 (-1 to 1)	0 (-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]

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:

[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	258	254	254	
Units: 10^9/L				
arithmetic mean (full range (min-max))	-0.01 (-0.93 to 0.45)	-0.001 (-0.34 to 0.33)	0.001 (-0.52 to 0.58)	

Statistical analyses

No statistical analyses for this end point

Primary: Eosinophils/Leukocytes (Change from baseline)

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

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:

[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	258	254	254	
Units: percent				
arithmetic mean (full range (min-max))	-0.2 (-12 to 6)	-0.1 (-5 to 7)	0 (-11 to 8)	

Statistical analyses

No statistical analyses for this end point

Primary: Erythrocytes (Change from baseline)

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

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:

[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	258	254	254	
Units: 10^12/L				
arithmetic mean (full range (min-max))	0.008 (-0.83 to 1.82)	0.001 (-0.77 to 1.16)	0.025 (-0.98 to 1.07)	

Statistical analyses

No statistical analyses for this end point

Primary: Hematocrit (Change from baseline)

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

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:

[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	258	254	254	
Units: percent				
arithmetic mean (full range (min-max))	0.11 (-9.8 to 8.8)	0.21 (-10.3 to 11.2)	0.24 (-8.3 to 7)	

Statistical analyses

No statistical analyses for this end point

Primary: Hemoglobin (Change from baseline)

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

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:

[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	258	254	254	
Units: g/dL				
arithmetic mean (full range (min-max))	-0.04 (-3.6 to 2.4)	-0.03 (-2.5 to 3.8)	-0.01 (-2.7 to 2.3)	

Statistical analyses

No statistical analyses for this end point

Primary: Leukocytes (Change from baseline)

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

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:

[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	258	254	254	
Units: 10^9/L				
arithmetic mean (full range (min-max))	0 (-6.8 to 5.67)	0.255 (-6.1 to 9.9)	-0.063 (-8.1 to 8.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Lymphocytes (Change from baseline)

End point title	Lymphocytes (Change from baseline)[10]

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:

[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	258	254	254	
Units: 10^9/L				
arithmetic mean (full range (min-max))	-0.019 (-1.96 to 1.75)	0.028 (-1.54 to 1.96)	-0.03 (-2.33 to 2.3)	

Statistical analyses

No statistical analyses for this end point

Primary: Lymphocytes/Leukocytes (Change from baseline)

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

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:

[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	258	254	254	
Units: percent				
arithmetic mean (full range (min-max))	-0.7 (-26 to 24)	-0.6 (-25 to 18)	-0.3 (-30 to 21)	

Statistical analyses

No statistical analyses for this end point

Primary: Monocytes (Change from baseline)

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

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:

[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	258	254	254	
Units: 10^9/L				
arithmetic mean (full range (min-max))	0.006 (-1 to 0.69)	0.018 (-0.62 to 0.81)	-0.018 (-0.89 to 0.73)	

Statistical analyses

No statistical analyses for this end point

Primary: Monocytes/Leukocytes (Change from baseline)

End point title	Monocytes/Leukocytes (Change from baseline)[13]

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:

[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	258	254	254	
Units: percent				
arithmetic mean (full range (min-max))	0.1 (-10 to 15)	-0.1 (-10 to 5)	-0.3 (-10 to 12)	

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 (± 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	258	254	254	
Units: 10^9/L				
arithmetic mean (full range (min-max))	0.021 (-7.02 to 4.78)	0.214 (-4.48 to 9.65)	-0.009 (-6.72 to 7.86)	

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 (± 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	258	254	254	
Units: percent				
arithmetic mean (full range (min-max))	0.8 (-29 to 32)	0.7 (-25 to 35)	0.7 (-22 to 39)	

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 (± 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	258	254	254	
Units: 10^9/L				
arithmetic mean (full range (min-max))	0.2 (-195 to 68)	0.3 (-198 to 159)	4 (-114 to 84)	

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 (± 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	258	254	254	
Units: IU/L				
arithmetic mean (full range (min-max))	1.1 (-87 to 109)	-1 (-99 to 57)	-2.4 (-185 to 100)	

Statistical analyses

No statistical analyses for this end point

Primary: Albumin (Change from baseline)

End point title	Albumin (Change from baseline)[18]

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:

[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	258	254	254	
Units: g/dL				
arithmetic mean (full range (min-max))	-0.02 (-0.6 to 0.8)	-0.03 (-0.8 to 0.7)	0.02 (-1.1 to 1)	

Statistical analyses

No statistical analyses for this end point

Primary: Alkaline Phosphatase (Change from baseline)

End point title	Alkaline Phosphatase (Change from baseline)[19]

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:

[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	258	254	254	
Units: IU/L				
arithmetic mean (full range (min-max))	-0.5 (-51 to 69)	-3.8 (-62 to 48)	-0.8 (-136 to 62)	

Statistical analyses

No statistical analyses for this end point

Primary: Aspartate Aminotransferase (Change from baseline)

End point title	Aspartate Aminotransferase (Change from baseline)[20]

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:

[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	258	254	254	
Units: IU/L				
arithmetic mean (full range (min-max))	0.5 (-51 to 60)	-0.7 (-71 to 91)	-1.2 (-97 to 78)	

Statistical analyses

No statistical analyses for this end point

Primary: Bicarbonate (Change from baseline)

End point title	Bicarbonate (Change from baseline)[21]

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:

[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	258	254	254	
Units: mEq/L				
arithmetic mean (full range (min-max))	-0.4 (-10 to 8)	-0.5 (-8 to 5)	-0.5 (-10 to 6)	

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 (± 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	258	254	254	
Units: mg/dL				
arithmetic mean (full range (min-max))	-0.01 (-0.7 to 1.3)	0 (-0.8 to 1)	-0.01 (-1 to 0.7)	

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 (± 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	258	254	254	
Units: mg/dL				
arithmetic mean (full range (min-max))	-0.5 (-11 to 11)	0 (-14 to 12)	0.2 (-9 to 13)	

Statistical analyses

No statistical analyses for this end point

Primary: Calcium (Change from baseline)

End point title	Calcium (Change from baseline)[24]

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:

[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	258	254	254	
Units: mg/dL				
arithmetic mean (full range (min-max))	-0.01 (-1 to 1.2)	-0.04 (-1 to 1.3)	0.01 (-1.5 to 1.2)	

Statistical analyses

No statistical analyses for this end point

Primary: Chloride (Change from baseline)

End point title	Chloride (Change from baseline)[25]

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:

[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	258	254	254	
Units: mEq/L				
arithmetic mean (full range (min-max))	-0.4 (-9 to 7)	-0.2 (-36 to 7)	-0.5 (-7 to 11)	

Statistical analyses

No statistical analyses for this end point

Primary: Creatine Phosphokinase (Change from baseline)

End point title	Creatine Phosphokinase (Change from baseline)[26]

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:

[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	258	254	254	
Units: IU/L				
arithmetic mean (full range (min-max))	-5.1 (-1561 to 968)	-7.8 (-2828 to 3159)	-22.1 (-4919 to 1616)	

Statistical analyses

No statistical analyses for this end point

Primary: Creatinine (Change from baseline)

End point title	Creatinine (Change from baseline)[27]

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:

[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	258	254	254	
Units: mg/dL				
arithmetic mean (full range (min-max))	0.008 (-0.39 to 0.4)	-0.001 (-0.37 to 0.4)	-0.014 (-0.24 to 0.19)	

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]

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:

[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	258	254	254	
Units: IU/L				
arithmetic mean (full range (min-max))	1.2 (-212 to 92)	0.5 (-62 to 46)	-2.2 (-781 to 259)	

Statistical analyses

No statistical analyses for this end point

Primary: Glucose (Change from baseline)

End point title	Glucose (Change from baseline)[29]

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:

[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	258	254	254	
Units: mg/dL				
arithmetic mean (full range (min-max))	0.2 (-164 to 65)	1.6 (-88 to 106)	4.5 (-50 to 209)	

Statistical analyses

No statistical analyses for this end point

Primary: Magnesium (Change from baseline)

End point title	Magnesium (Change from baseline)[30]

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:

[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	258	254	254	
Units: mg/dL				
arithmetic mean (full range (min-max))	0.01 (-0.5 to 1.8)	-0.02 (-0.5 to 0.4)	-0.02 (-0.7 to 0.3)	

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	258	254	254	
Units: mg/dL				
arithmetic mean (full range (min-max))	0.02 (-1.8 to 2.4)	-0.06 (-1.5 to 1.9)	0 (-1.6 to 2.5)	

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	258	254	254	
Units: mEq/L				
arithmetic mean (full range (min-max))	0.05 (-1.1 to 1.4)	0.01 (-1.4 to 1)	0.02 (-1.4 to 1.1)	

Statistical analyses

No statistical analyses for this end point

Primary: Protein (Change from baseline)

End point title	Protein (Change from baseline)[33]

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:

[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	258	254	254	
Units: g/dL				
arithmetic mean (full range (min-max))	-0.05 (-1.2 to 1.1)	-0.11 (-1.5 to 0.9)	-0.01 (-1.9 to 1.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Sodium (Change from baseline)

End point title	Sodium (Change from baseline)[34]

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:

[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	258	254	254	
Units: mEq/L				
arithmetic mean (full range (min-max))	0 (-10 to 7)	0.3 (-18 to 9)	0 (-6 to 9)	

Statistical analyses

No statistical analyses for this end point

Primary: Urate (Change from baseline)

End point title	Urate (Change from baseline)[35]

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:

[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	258	254	254	
Units: mg/dL				
arithmetic mean (full range (min-max))	0.05 (-2.8 to 2.6)	0.06 (-3.5 to 3.3)	0.05 (-3.2 to 3.8)	

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]

End point description:

End point type	Primary

End point timeframe:

At the screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: mmHg				
arithmetic mean (full range (min-max))	0.5 (-35 to 40)	0.4 (-22 to 31)	1.9 (-23 to 38)	

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]

End point description:

End point type	Primary

End point timeframe:

At the screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: mmHg				
arithmetic mean (full range (min-max))	0 (-20 to 25)	-0.2 (-23 to 26)	0.7 (-17 to 28)	

Statistical analyses

No statistical analyses for this end point

Primary: Pulse Rate (Change from baseline)

End point title	Pulse Rate (Change from baseline)[38]

End point description:

End point type	Primary

End point timeframe:

At the screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: BEATS/MIN				
arithmetic mean (full range (min-max))	-1 (-29 to 50)	1.3 (-23 to 30)	0.2 (-25 to 37)	

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:

At the screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: BREATHS/MIN				
arithmetic mean (full range (min-max))	-0.1 (-5 to 6)	0.2 (-4 to 8)	0.1 (-13 to 4)	

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:

At the screening visit, on Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: Celsius				
arithmetic mean (full range (min-max))	0 (-1.1 to 1.2)	0.01 (-1 to 1)	-0.03 (-1 to 1)	

Statistical analyses

No statistical analyses for this end point

Primary: Weight (Change from baseline)

End point title	Weight (Change from baseline)[41]

End point description:

End point type	Primary

End point timeframe:

On Day 1 (pre-dose) and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: kg				
arithmetic mean (full range (min-max))	0.31 (-10.3 to 17.1)	0.28 (-12.1 to 12)	0.53 (-11.6 to 19.5)	

Statistical analyses

No statistical analyses for this end point

Primary: Heart Rate (Change from baseline)

End point title	Heart Rate (Change from baseline)[42]

End point description:

End point type	Primary

End point timeframe:

At screening visit, Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: BEATS/MIN				
arithmetic mean (full range (min-max))	0.3 (-35 to 50)	2 (-19 to 50)	0.8 (-28 to 46)	

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:

At screening visit, Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: msec				
arithmetic mean (full range (min-max))	-1.2 (-72 to 65)	-2.6 (-58 to 69)	-0.8 (-86 to 58)	

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:

At screening visit, Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: msec				
arithmetic mean (full range (min-max))	0.1 (-68 to 53)	2.4 (-48 to 70)	1.3 (-64 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

End point description:

End point type	Primary

End point timeframe:

At screening visit, Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: msec				
arithmetic mean (full range (min-max))	-0.3 (-61 to 42)	0.6 (-37 to 43)	0.6 (-55 to 51)	

Statistical analyses

No statistical analyses for this end point

Primary: QRS Duration (Change from baseline)

End point title	QRS Duration (Change from baseline)[46]

End point description:

End point type	Primary

End point timeframe:

At screening visit, Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: msec				
arithmetic mean (full range (min-max))	-0.5 (-19 to 20)	0.6 (-15 to 18)	-0.4 (-69 to 24)	

Statistical analyses

No statistical analyses for this end point

Primary: PR Duration (Change from baseline)

End point title	PR Duration (Change from baseline)[47]

End point description:

End point type	Primary

End point timeframe:

At screening visit, Day 1 pre-dose and within 3 hours post-dose, and on Days 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: msec				
arithmetic mean (full range (min-max))	-1.2 (-83 to 41)	-1.6 (-55 to 39)	0.2 (-30 to 48)	

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]

End point description:

End point type	Primary

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	258	254	254	
Units: n/a				
arithmetic mean (full range (min-max))	1.2 (0 to 16)	1 (0 to 10)	1.2 (0 to 21)	

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]

End point description:

End point type	Primary

End point timeframe:

Screening, Days 1 (pre-dose), 14 (telephone call), 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: Subjects with suicidal behavior/ideation	1	0	1	

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]

End point description:

End point type	Primary

End point timeframe:

Screening, Days 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (± 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	258	254	254	
Units: n/a				
arithmetic mean (full range (min-max))	0 (-4 to 7)	-0.2 (-5 to 2)	-0.1 (-3 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]

End point description:

End point type	Primary

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	258	254	254	
Units: n/a				
arithmetic mean (full range (min-max))	-1.1 (-12 to 15)	-1.3 (-10 to 21)	-1.3 (-14 to 10)	

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)

End point description:

End point type	Secondary

End point timeframe:

On 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	255	251	250	
Units: n/a				
arithmetic mean (full range (min-max))	-1.9 (-14 to 11)	-2.1 (-15 to 10)	-1.7 (-15 to 9)	

Statistical analyses

Statistical analysis title	Hochberg method adjustment
Comparison groups	EVP-6124, 2 mg v EVP-6124, 1 mg v Placebo
Number of subjects included in analysis	756
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Hochberg method adjustment

Secondary: MATRICS Consensus Cognition Battery (MCCB) Overall Composite T-Scores with imputation of missing components (Change from baseline)

End point title	MATRICS Consensus Cognition 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	255	251	250	
Units: n/a				
arithmetic mean (standard error)	2.9 (± 0.41)	2.9 (± 0.45)	2.8 (± 0.43)	

Statistical analyses

No statistical analyses for this end point

Secondary: MATRICS Consensus Cognition Battery (MCCB) Overall Composite T-Scores without imputation of missing components (Change from baseline)

End point title	MATRICS Consensus Cognition Battery (MCCB) Overall Composite T-Scores without 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	255	251	250	
Units: n/a				
arithmetic mean (full range (min-max))	3 (-15 to 15)	3.3 (-13 to 26)	2.8 (-18 to 17)	

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:

On 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	255	251	250	
Units: n/a				
arithmetic mean (full range (min-max))	-0.7 (-5 to 4)	-0.6 (-4 to 3)	-0.8 (-4 to 4)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

On 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	255	251	250	
Units: n/a				
arithmetic mean (full range (min-max))	-1.8 (-12 to 10)	-2 (-14 to 10)	-1.5 (-11 to 12)	

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)

End point description:

End point type	Secondary

End point timeframe:

On Days 1 (predose, 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	255	251	250	
Units: n/a				
arithmetic mean (full range (min-max))	3.2 (1 to 5)	3.2 (1 to 6)	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)

End point description:

End point type	Secondary

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	255	251	250	
Units: n/a				
arithmetic mean (full range (min-max))	3.3 (1 to 6)	3.3 (1 to 6)	3.3 (1 to 6)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Concentration of EVP-6124 (Day 182)

End point title	Concentration of EVP-6124 (Day 182)[52]

End point description:

End point type	Other pre-specified

End point timeframe:

Day 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (± 2 days) or ET.

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The concentration of EVP-6124 was not reported in the placebo arm.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	250		
Units: ng/mL				
arithmetic mean (full range (min-max))	1.7286 (0 to 5.94)	3.2306 (0 to 9.48)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Concentration of EVP-6124 N-oxide (Day 182)

End point title	Concentration of EVP-6124 N-oxide (Day 182)[53]

End point description:

End point type	Other pre-specified

End point timeframe:

Day 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (± 2 days) or ET.

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The concentration of EVP-6124 N-oxide was not reported in the placebo arm.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	250		
Units: ng/mL				
arithmetic mean (full range (min-max))	0.1752 (0 to 0.629)	0.3242 (0 to 0.917)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Concentration of EVP-6124 Acid Metabolite (Day 182)

End point title	Concentration of EVP-6124 Acid Metabolite (Day 182)[54]

End point description:

End point type	Other pre-specified

End point timeframe:

Day 1 (pre-dose), 28, 56, 84, 112, 140, and 182 (± 2 days) or ET.

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The concentration of EVP-6124 Acid Metabolite was not reported in the placebo arm.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	250		
Units: ng/mL				
arithmetic mean (full range (min-max))	0.2584 (0 to 0.942)	0.4645 (0 to 2.58)		

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

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	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 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).

Serious adverse events	EVP-6124, 1 mg	Placebo	EVP-6124, 2 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 258 (4.26%)	7 / 254 (2.76%)	7 / 254 (2.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
ECG signs of myocardial ischaemia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences causally related to treatment / all	1 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			

subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences causally related to treatment / all	0 / 11	0 / 7	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychiatric decompensation			
subjects affected / exposed	6 / 258 (2.33%)	5 / 254 (1.97%)	4 / 254 (1.57%)
occurrences causally related to treatment / all	1 / 11	0 / 7	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance abuse			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Suicidal ideation			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Stag horn calculus			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Dengue fever			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 7	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	Placebo	EVP-6124, 2 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 258 (49.22%)	148 / 254 (58.27%)	127 / 254 (50.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Vascular disorders			
Hypertension			

subjects affected / exposed	4 / 258 (1.55%)	4 / 254 (1.57%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hypotension			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 258 (1.16%)	1 / 254 (0.39%)	3 / 254 (1.18%)
occurrences (all)	127	148	127
Asthenia			
subjects affected / exposed	2 / 258 (0.78%)	3 / 254 (1.18%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Non-cardiac chest pain			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Pyrexia			
subjects affected / exposed	1 / 258 (0.39%)	2 / 254 (0.79%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Oedema peripheral			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Chills			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Malaise			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Dysfunctional uterine bleeding			

subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Dysmenorrhoea			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Lactation disorder			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	1448	127
Menopausal symptoms			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Menstrual disorder			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Ovarian cyst			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 258 (0.39%)	2 / 254 (0.79%)	3 / 254 (1.18%)
occurrences (all)	127	148	127
Asthma			
subjects affected / exposed	2 / 258 (0.78%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Nasal congestion			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Wheezing			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Sinus congestion			
subjects affected / exposed	0 / 258 (0.00%)	2 / 254 (0.79%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Sleep apnoea syndrome			

subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Dyspnoea			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Epistaxis			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Haemoptysis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Productive cough			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Respiratory disorder			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Respiratory tract congestion			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Sneezing			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Throat irritation			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Tonsillar hypertrophy			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Psychiatric disorders			
Psychiatric decompensation			
subjects affected / exposed	10 / 258 (3.88%)	9 / 254 (3.54%)	9 / 254 (3.54%)
occurrences (all)	127	148	127
Insomnia			
subjects affected / exposed	8 / 258 (3.10%)	11 / 254 (4.33%)	7 / 254 (2.76%)
occurrences (all)	127	148	127

Anxiety			
subjects affected / exposed	9 / 258 (3.49%)	5 / 254 (1.97%)	8 / 254 (3.15%)
occurrences (all)	127	148	127
Irritability			
subjects affected / exposed	3 / 258 (1.16%)	4 / 254 (1.57%)	3 / 254 (1.18%)
occurrences (all)	127	148	127
Depression			
subjects affected / exposed	1 / 258 (0.39%)	3 / 254 (1.18%)	4 / 254 (1.57%)
occurrences (all)	127	148	127
Tension			
subjects affected / exposed	3 / 258 (1.16%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Suicidal ideation			
subjects affected / exposed	0 / 258 (0.00%)	2 / 254 (0.79%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Agitation			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Depressed mood			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Panic attack			
subjects affected / exposed	0 / 258 (0.00%)	2 / 254 (0.79%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Psychotic disorder			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Schizophrenia			
subjects affected / exposed	2 / 258 (0.78%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Sleep disorder			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Abnormal dreams			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127

Affect lability			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Confusional state			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Depressive symptom			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Disturbance in social behaviour			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Drug abuse			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Dysphoria			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Emotional disorder			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hallucination			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Homicidal ideation			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Initial insomnia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Middle insomnia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Mood swings			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127

Somnambulism			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Substance abuse			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Suicide attempt			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Investigations			
Weight increased			
subjects affected / exposed	6 / 258 (2.33%)	10 / 254 (3.94%)	6 / 254 (2.36%)
occurrences (all)	127	148	127
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 258 (1.55%)	12 / 254 (4.72%)	5 / 254 (1.97%)
occurrences (all)	127	148	127
Alanine aminotransferase increased			
subjects affected / exposed	2 / 258 (0.78%)	5 / 254 (1.97%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 258 (0.78%)	4 / 254 (1.57%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 258 (0.78%)	3 / 254 (1.18%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Weight decreased			
subjects affected / exposed	3 / 258 (1.16%)	0 / 254 (0.00%)	4 / 254 (1.57%)
occurrences (all)	127	148	127
Blood pressure increased			
subjects affected / exposed	0 / 258 (0.00%)	2 / 254 (0.79%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Blood creatinine increased			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Blood glucose increased			

subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Electrocardiogram T wave amplitude decreased			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Blood cholesterol increased			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Cardiac murmur			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Drug screen positive			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
ECG signs of myocardial ischaemia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Electrocardiogram T wave abnormal			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Electrocardiogram abnormal			

subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Haematocrit increased			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Haemoglobin decreased			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Haemoglobin increased			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Neutrophil count decreased			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Red blood cell count increased			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Red blood cells urine			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Urinary casts			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Urine leukocyte esterase positive			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
White blood cell count increased			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
White blood cells urine positive			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Injury, poisoning and procedural complications			
Ligament sprain			

subjects affected / exposed	2 / 258 (0.78%)	4 / 254 (1.57%)	3 / 254 (1.18%)
occurrences (all)	127	148	127
Laceration			
subjects affected / exposed	0 / 258 (0.00%)	2 / 254 (0.79%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Muscle strain			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Road traffic accident			
subjects affected / exposed	0 / 258 (0.00%)	2 / 254 (0.79%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Contusion			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Animal bite			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Ankle fracture			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Arthropod bite			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Back injury			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Burns second degree			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Craniocerebral injury			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Epicondylitis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Eye injury			

subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Foot fracture			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hand fracture			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Head injury			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hip fracture			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Human bite			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Joint dislocation			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Limb injury			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Lip injury			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Multiple injuries			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Scratch			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Skin abrasion			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Soft tissue injury			

subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Tooth fracture			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Palpitations			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Tachycardia			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Bradycardia			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Defect conduction intraventricular			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Myocardial infarction			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Tachycardia paroxysmal			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 258 (5.04%)	15 / 254 (5.91%)	18 / 254 (7.09%)
occurrences (all)	127	148	127
Dizziness			
subjects affected / exposed	6 / 258 (2.33%)	5 / 254 (1.97%)	5 / 254 (1.97%)
occurrences (all)	127	148	127
Somnolence			

subjects affected / exposed	3 / 258 (1.16%)	1 / 254 (0.39%)	6 / 254 (2.36%)
occurrences (all)	127	148	127
Tremor			
subjects affected / exposed	3 / 258 (1.16%)	4 / 254 (1.57%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Akathisia			
subjects affected / exposed	2 / 258 (0.78%)	2 / 254 (0.79%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Paraesthesia			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Extrapyramidal disorder			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Sciatica			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Sedation			
subjects affected / exposed	0 / 258 (0.00%)	2 / 254 (0.79%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Cognitive disorder			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Cogwheel rigidity			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Convulsion			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Cubital tunnel syndrome			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Drooling			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Dyskinesia			

subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hypokinesia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Loss of consciousness			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Parkinsonism			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Poor quality sleep			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Presyncope			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Psychomotor hyperactivity			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Radiculitis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Neutropenia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Eosinophilia			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Iron deficiency anaemia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127

Lymphadenopathy			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Polycythaemia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 258 (0.78%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Ear discomfort			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Ear canal erythema			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 258 (0.00%)	2 / 254 (0.79%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Blepharospasm			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Eye irritation			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Eye pain			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Visual acuity reduced			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Vitreous floaters			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	14 / 258 (5.43%)	8 / 254 (3.15%)	17 / 254 (6.69%)
occurrences (all)	127	148	127
Diarrhoea			
subjects affected / exposed	2 / 258 (0.78%)	8 / 254 (3.15%)	6 / 254 (2.36%)
occurrences (all)	127	148	127
Dyspepsia			
subjects affected / exposed	4 / 258 (1.55%)	1 / 254 (0.39%)	7 / 254 (2.76%)
occurrences (all)	127	148	127
Vomiting			
subjects affected / exposed	2 / 258 (0.78%)	7 / 254 (2.76%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Toothache			
subjects affected / exposed	4 / 258 (1.55%)	2 / 254 (0.79%)	3 / 254 (1.18%)
occurrences (all)	127	148	127
Nausea			
subjects affected / exposed	5 / 258 (1.94%)	1 / 254 (0.39%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Abdominal pain upper			
subjects affected / exposed	2 / 258 (0.78%)	4 / 254 (1.57%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Abdominal pain			
subjects affected / exposed	2 / 258 (0.78%)	2 / 254 (0.79%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Dry mouth			
subjects affected / exposed	1 / 258 (0.39%)	2 / 254 (0.79%)	3 / 254 (1.18%)
occurrences (all)	127	148	127
Abdominal discomfort			
subjects affected / exposed	3 / 258 (1.16%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Gingival pain			
subjects affected / exposed	2 / 258 (0.78%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Flatulence			
subjects affected / exposed	2 / 258 (0.78%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Abdominal distension			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Abdominal rigidity			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Anal fissure			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Dental caries			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Epigastric discomfort			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Gastritis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Gastrointestinal pain			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Gingival hyperplasia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Large intestine polyp			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Oral disorder			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Pancreatitis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127

Salivary hypersecretion			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hepatobiliary disorders			
Chronic hepatitis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hepatitis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Liver disorder			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Dermatitis contact			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Acne			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Blood blister			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Dermatitis allergic			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Eczema			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Exfoliative rash			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hyperkeratosis			

subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Pruritus			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Rash			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Rosacea			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Skin reaction			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Renal and urinary disorders			
Bladder dysfunction			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Calculus urinary			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Enuresis			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Nephrolithiasis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Stag horn calculus			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Urge incontinence			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Endocrine disorders			
Hyperprolactinaemia			

subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 258 (1.55%)	13 / 254 (5.12%)	6 / 254 (2.36%)
occurrences (all)	127	148	127
Pain in extremity			
subjects affected / exposed	1 / 258 (0.39%)	6 / 254 (2.36%)	4 / 254 (1.57%)
occurrences (all)	127	148	127
Arthralgia			
subjects affected / exposed	4 / 258 (1.55%)	2 / 254 (0.79%)	4 / 254 (1.57%)
occurrences (all)	127	148	127
Musculoskeletal pain			
subjects affected / exposed	4 / 258 (1.55%)	2 / 254 (0.79%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Myalgia			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Neck pain			
subjects affected / exposed	1 / 258 (0.39%)	3 / 254 (1.18%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Muscle spasms			
subjects affected / exposed	1 / 258 (0.39%)	2 / 254 (0.79%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Musculoskeletal stiffness			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Muscle twitching			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Costochondritis			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Flank pain			

subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Groin pain			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Pain in jaw			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Plantar fascial fibromatosis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Plantar fasciitis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Rotator cuff syndrome			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 258 (2.71%)	11 / 254 (4.33%)	8 / 254 (3.15%)
occurrences (all)	127	148	127
Influenza			
subjects affected / exposed	1 / 258 (0.39%)	6 / 254 (2.36%)	3 / 254 (1.18%)
occurrences (all)	127	148	127
Upper respiratory tract infection			
subjects affected / exposed	2 / 258 (0.78%)	3 / 254 (1.18%)	5 / 254 (1.97%)
occurrences (all)	127	148	127
Respiratory tract infection viral			
subjects affected / exposed	4 / 258 (1.55%)	2 / 254 (0.79%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Urinary tract infection			
subjects affected / exposed	2 / 258 (0.78%)	4 / 254 (1.57%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Bronchitis			
subjects affected / exposed	3 / 258 (1.16%)	2 / 254 (0.79%)	2 / 254 (0.79%)
occurrences (all)	127	148	127

Tooth abscess			
subjects affected / exposed	0 / 258 (0.00%)	3 / 254 (1.18%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Rhinitis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	2 / 254 (0.79%)
occurrences (all)	127	148	127
Cellulitis			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Gastroenteritis viral			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Pharyngitis			
subjects affected / exposed	1 / 258 (0.39%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Respiratory tract infection			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Tonsillitis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Abscess			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Acute sinusitis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Bacterial vaginosis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Dengue fever			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127

Diverticulitis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Eye infection			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Folliculitis			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Fungal skin infection			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Furuncle			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Gastroenteritis			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Herpes zoster			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Impetigo			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Laryngitis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Mononucleosis syndrome			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Otitis externa			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Parainfluenzae virus infection			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127

Pneumonia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Pyelonephritis chronic			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Sinusitis			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Subcutaneous abscess			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Tinea pedis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Tracheitis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Trichomoniasis			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	2 / 258 (0.78%)	3 / 254 (1.18%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Decreased appetite			
subjects affected / exposed	0 / 258 (0.00%)	2 / 254 (0.79%)	3 / 254 (1.18%)
occurrences (all)	127	148	127
Dehydration			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Diabetes mellitus			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hypercholesterolaemia			

subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Hyperglycaemia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 254 (0.00%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hyperphagia			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Hyperphosphataemia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127
Hypokalaemia			
subjects affected / exposed	0 / 258 (0.00%)	0 / 254 (0.00%)	1 / 254 (0.39%)
occurrences (all)	127	148	127
Overweight			
subjects affected / exposed	0 / 258 (0.00%)	1 / 254 (0.39%)	0 / 254 (0.00%)
occurrences (all)	127	148	127

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
26 August 2014	Protocol Amendment 2.1
30 September 2015	Protocol Amendment 3

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported