Clinical trial results:
A Multicenter 26-Week Extension Study to Evaluate the Safety and Clinical Effects of Prolonged Exposure to 1 and 2 mg Doses of EVP-6124, an Alpha- 7 Nicotinic Acetylcholine Receptor Agonist, as an Adjunctive Pro-cognitive Treatment in Subjects with Schizophrenia on Chronic Stable Atypical Antipsychotic Therapy

Summary

EudraCT number	2012-003228-19
Trial protocol	ES DE IT GB PL
Global end of trial date	16 October 2015

Results information

Result version number	v1 (current)
This version publication date	31 October 2016
First version publication date	31 October 2016

Trial information

Trial identification

Sponsor protocol code	EVP-6124-017

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	500 Arsenal Street, Watertown, MA, United States, 02472
Public contact	Regulatory Project Manager, INC Research, +44 1276481000, SM_Regaffairs_eu_ap@incresearch.com
Scientific contact	Regulatory Project Manager, INC Research, +44 1276481000, SM_Regaffairs_eu_ap@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	16 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety of 1 and 2 mg doses of EVP-6124 tablets administered once daily for up to 52 weeks in subjects who received EVP-6124 in both the pivotal and extension studies and up to 26 weeks in subjects who were randomized from placebo to EVP-6124 upon entry into this extension study.

Protection of trial subjects:

There were no specific measures as the only 'invasive' measures were blood sample analyses.

Background therapy:

Patients were enrolled into the antecedent studies (015 and 016) that were stably treated with atypical anti-psychotic agents. These are the standard treatment of choice for this patient population. Only the anti-psychotic clozapine was excluded. This was for two reasons: clozapine treated patients are uniquely ‘sicker’ as it remains a second or third line treatment choice and clozapine has safety concerns which require special monitoring procedures that would more difficult to incorporate into the studies.

Evidence for comparator: -

Actual start date of recruitment	13 June 2013
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: 23
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Argentina: 37
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Colombia: 29
Country: Number of subjects enrolled	Mexico: 25
Country: Number of subjects enrolled	Romania: 30
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	Serbia: 7
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Ukraine: 127
Country: Number of subjects enrolled	United States: 403

Worldwide total number of subjects	827
EEA total number of subjects	109

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)	827
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who completed double-blind treatment (ie, completion of the Day 182 Visit) in Studies EVP-6124-015 or EVP-6124-016 and who fulfilled all inclusion/exclusion criteria for this extension study were eligible for enrollment.

Pre-assignment period milestones

Number of subjects started	827
Number of subjects completed	827

Period 1

Period 1 title	Overall 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:

Subjects who received EVP-6124 during the previous study (EVP-6124-015 or EVP-6124-016) will remain on the same dose. Subjects who received placebo during the pivotal study (EVP-6124-015 or EVP-6124-016) will be randomized (1:1 ratio) to once daily EVP-6124 1 or 2 mg tablets for up to 26 weeks (Days 1-182).

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:

Throughout the study (Days 1-182), all subjects will be instructed to take 1 tablet of study medication once daily, preferably at the same time (between 8 to 10 AM if feasible) every morning, with an adequate amount of water with or without food (after morning meal is preferred).

Arm title	EVP-6124, 2 mg

Arm description:

Subjects who received EVP-6124 during the previous study (EVP-6124-015 or EVP-6124-016) will remain on the same dose. Subjects who received placebo during the pivotal study (EVP-6124-015 or EVP-6124-016) will be randomized (1:1 ratio) to once daily EVP-6124 1 or 2 mg tablets for up to 26 weeks (Days 1-182).

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:

Throughout the study (Days 1-182), all subjects will be instructed to take 1 tablet of study medication once daily, preferably at the same time (between 8 to 10 AM if feasible) every morning, with an adequate amount of water with or without food (after morning meal is preferred).

Number of subjects in period 1	EVP-6124, 1 mg	EVP-6124, 2 mg
Started	428	399
Completed	248	223
Not completed	180	176
Physician decision	1	1
Consent withdrawn by subject	14	12
Adverse event, non-fatal	13	17
Medication Prohibited by Protocol	2	1
Subject Incarceration	2	1
Substance Abuse	-	1
Sponsor Decision	136	129
Lost to follow-up	9	10
Protocol deviation	3	4

Baseline characteristics

Reporting groups	
Reporting group title	EVP-6124, 1 mg
Reporting group description:	
Subjects who received EVP-6124 during the previous study (EVP-6124-015 or EVP-6124-016) will remain on the same dose. Subjects who received placebo during the pivotal study (EVP-6124-015 or EVP-6124-016) will be randomized (1:1 ratio) to once daily EVP-6124 1 or 2 mg tablets for up to 26 weeks (Days 1-182).	
Reporting group title	EVP-6124, 2 mg
Reporting group description:	
Subjects who received EVP-6124 during the previous study (EVP-6124-015 or EVP-6124-016) will remain on the same dose. Subjects who received placebo during the pivotal study (EVP-6124-015 or EVP-6124-016) will be randomized (1:1 ratio) to once daily EVP-6124 1 or 2 mg tablets for up to 26 weeks (Days 1-182).	

Reporting group values	EVP-6124, 1 mg	EVP-6124, 2 mg	Total
Number of subjects	428	399	827
Age categorical Units: Subjects			
Adults (18-64 years)	428	399	827
Age continuous Units: years			
arithmetic mean	37.4	37	
full range (min-max)	18 to 51	18 to 51	-
Gender categorical Units: Subjects			
Female	151	138	289
Male	277	261	538

End points

End points reporting groups

Reporting group title	EVP-6124, 1 mg

Reporting group description:

Subjects who received EVP-6124 during the previous study (EVP-6124-015 or EVP-6124-016) will remain on the same dose. Subjects who received placebo during the pivotal study (EVP-6124-015 or EVP-6124-016) will be randomized (1:1 ratio) to once daily EVP-6124 1 or 2 mg tablets for up to 26 weeks (Days 1-182).

Reporting group title	EVP-6124, 2 mg

Reporting group description:

Subjects who received EVP-6124 during the previous study (EVP-6124-015 or EVP-6124-016) will remain on the same dose. Subjects who received placebo during the pivotal study (EVP-6124-015 or EVP-6124-016) will be randomized (1:1 ratio) to once daily EVP-6124 1 or 2 mg tablets for up to 26 weeks (Days 1-182).

Primary: Treatment emergent adverse events (TEAEs)

End point title	Treatment emergent adverse events (TEAEs)[1]

End point description:

End point type	Primary

End point timeframe:

Throughout the study

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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: Subjects with any TEAEs	164	149		

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)[2]

End point description:

End point type	Primary

End point timeframe:

On Days 14, 28, 56, 84, 112, 140, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: Subjects who had any suicidal ideation	4	1		

Statistical analyses

No statistical analyses for this end point

Primary: Calgary Depression Scale for Schizophrenia (CDSS) (change from baseline)

End point title	Calgary Depression Scale for Schizophrenia (CDSS) (change from baseline)[3]

End point description:

End point type	Primary

End point timeframe:

The CDSS will be completed at Day 182 or ET. The CDSS was performed at the final study visit (Day 182) for the previous study (EVP-6124-015 or EVP-6124-016), and this value will serve as the baseline assessment.

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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: n/a				
arithmetic mean (full range (min-max))	-0.1 (-12 to 10)	0 (-9 to 9)		

Statistical analyses

No statistical analyses for this end point

Primary: Simpson-Angus Scale (SAS) (change from baseline)

End point title	Simpson-Angus Scale (SAS) (change from baseline)[4]

End point description:

End point type	Primary

End point timeframe:

On Days 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: n/a				
arithmetic mean (full range (min-max))	0 (-4 to 4)	0 (-4 to 3)		

Statistical analyses

No statistical analyses for this end point

Primary: Heart rate (change from baseline)

End point title	Heart rate (change from baseline)[5]

End point description:

End point type	Primary

End point timeframe:

On Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: beats/min				
arithmetic mean (full range (min-max))	2.1 (-42 to 43)	0.4 (-39 to 37)		

Statistical analyses

No statistical analyses for this end point

Primary: QT duration (change from baseline)

End point title	QT duration (change from baseline)[6]

End point description:

End point type	Primary

End point timeframe:

On Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: msec				
arithmetic mean (full range (min-max))	-3.5 (-87 to 83)	-1.2 (-82 to 88)		

Statistical analyses

No statistical analyses for this end point

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

End point title	QTcF - Fridericia's Correction (change from baseline)[7]

End point description:

End point type	Primary

End point timeframe:

On Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: msec				
arithmetic mean (full range (min-max))	0 (-49 to 50)	-0.8 (-43 to 61)		

Statistical analyses

No statistical analyses for this end point

Primary: QRS Duration (change from baseline)

End point title	QRS Duration (change from baseline)[8]

End point description:

End point type	Primary

End point timeframe:

On Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: msec				
arithmetic mean (full range (min-max))	0.1 (-23 to 22)	0.2 (-21 to 19)		

Statistical analyses

No statistical analyses for this end point

Primary: PR Duration (change from baseline)

End point title	PR Duration (change from baseline)[9]

End point description:

End point type	Primary

End point timeframe:

On Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: msec				
arithmetic mean (full range (min-max))	-2 (-65 to 73)	0.5 (-26 to 51)		

Statistical analyses

No statistical analyses for this end point

Primary: RR duration (change from baseline)

End point title	RR duration (change from baseline)[10]

End point description:

End point type	Primary

End point timeframe:

On Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: msec				
arithmetic mean (full range (min-max))	-22.7 (-472 to 468)	-2 (-567 to 346)		

Statistical analyses

No statistical analyses for this end point

Primary: Basophils (change from baseline)

End point title	Basophils (change from baseline)[11]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: 10^9/L				
arithmetic mean (full range (min-max))	0.001 (-0.09 to 0.1)	0 (-0.05 to 0.08)		

Statistical analyses

No statistical analyses for this end point

Primary: Eosinophils (change from baseline)

End point title	Eosinophils (change from baseline)[12]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: 10^9/L				
arithmetic mean (full range (min-max))	-0.005 (-0.44 to 0.4)	-0.008 (-0.63 to 0.56)		

Statistical analyses

No statistical analyses for this end point

Primary: Erythrocytes (change from baseline)

End point title	Erythrocytes (change from baseline)[13]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: 10^12/L				
arithmetic mean (full range (min-max))	-0.009 (-1.03 to 1.79)	0.018 (-1.02 to 2.46)		

Statistical analyses

No statistical analyses for this end point

Primary: Hematocrit (change from baseline)

End point title	Hematocrit (change from baseline)[14]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: percent				
arithmetic mean (full range (min-max))	0.23 (-7.8 to 15.4)	0.23 (-10.5 to 12.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Hemoglobin (change from baseline)

End point title	Hemoglobin (change from baseline)[15]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: g/dL				
arithmetic mean (full range (min-max))	0.01 (-3 to 5.2)	0 (-4.1 to 3.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Leukocytes (change from baseline)

End point title	Leukocytes (change from baseline)[16]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: 10^9/L				
arithmetic mean (full range (min-max))	0.023 (-5.66 to 6.84)	-0.094 (-5.3 to 5.75)		

Statistical analyses

No statistical analyses for this end point

Primary: Lymphocytes (change from baseline)

End point title	Lymphocytes (change from baseline)[17]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: 10^9/L				
arithmetic mean (full range (min-max))	0.027 (-1.5 to 2.1)	0.004 (-1.34 to 2.16)		

Statistical analyses

No statistical analyses for this end point

Primary: Monocytes (change from baseline)

End point title	Monocytes (change from baseline)[18]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: 10^9/L				
arithmetic mean (full range (min-max))	-0.021 (-0.78 to 0.66)	-0.018 (-0.6 to 0.41)		

Statistical analyses

No statistical analyses for this end point

Primary: Neutrophils (change from baseline)

End point title	Neutrophils (change from baseline)[19]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: 10^9/L				
arithmetic mean (full range (min-max))	0.01 (-6.6 to 6.64)	-0.112 (-4.75 to 4.42)		

Statistical analyses

No statistical analyses for this end point

Primary: Platelets (change from baseline)

End point title	Platelets (change from baseline)[20]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: 10^9/L				
arithmetic mean (full range (min-max))	0.6 (-126 to 225)	0.2 (-145 to 162)		

Statistical analyses

No statistical analyses for this end point

Primary: Alanine Aminotransferase (change from baseline)

End point title	Alanine Aminotransferase (change from baseline)[21]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: IU/L				
arithmetic mean (full range (min-max))	-0.4 (-67 to 112)	1.2 (-87 to 234)		

Statistical analyses

No statistical analyses for this end point

Primary: Albumin (change from baseline)

End point title	Albumin (change from baseline)[22]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: g/dL				
arithmetic mean (full range (min-max))	-0.03 (-0.9 to 1.1)	-0.05 (-0.9 to 0.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Alkaline Phosphatase (change from baseline)

End point title	Alkaline Phosphatase (change from baseline)[23]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: IU/L				
arithmetic mean (full range (min-max))	-1 (-51 to 85)	0.5 (-91 to 57)		

Statistical analyses

No statistical analyses for this end point

Primary: Aspartate Aminotransferase (change from baseline)

End point title	Aspartate Aminotransferase (change from baseline)[24]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: IU/L				
arithmetic mean (full range (min-max))	0.5 (-56 to 217)	1 (-74 to 111)		

Statistical analyses

No statistical analyses for this end point

Primary: Bicarbonate (change from baseline)

End point title	Bicarbonate (change from baseline)[25]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mEq/L				
arithmetic mean (full range (min-max))	-0.5 (-9 to 8)	-0.5 (-7 to 6)		

Statistical analyses

No statistical analyses for this end point

Primary: Bilirubin (change from baseline)

End point title	Bilirubin (change from baseline)[26]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mg/dL				
arithmetic mean (full range (min-max))	0.02 (-0.5 to 2.3)	-0.01 (-1.1 to 1.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Blood Urea Nitrogen (change from baseline)

End point title	Blood Urea Nitrogen (change from baseline)[27]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mg/dL				
arithmetic mean (full range (min-max))	0 (-8 to 25)	-0.4 (-16 to 9)		

Statistical analyses

No statistical analyses for this end point

Primary: Calcium (change from baseline)

End point title	Calcium (change from baseline)[28]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mg/dL				
arithmetic mean (full range (min-max))	-0.01 (-1.2 to 1.7)	0.01 (-1.2 to 1.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Chloride (change from baseline)

End point title	Chloride (change from baseline)[29]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mEq/L				
arithmetic mean (full range (min-max))	-0.2 (-17 to 8)	-0.1 (-10 to 6)		

Statistical analyses

No statistical analyses for this end point

Primary: Creatine Kinase (change from baseline)

End point title	Creatine Kinase (change from baseline)[30]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: IU/L				
arithmetic mean (full range (min-max))	29.9 (-953 to 4605)	8.9 (-1359 to 4853)		

Statistical analyses

No statistical analyses for this end point

Primary: Creatinine (change from baseline)

End point title	Creatinine (change from baseline)[31]

End point description:

End point type	Primary

End point timeframe:

Visits 1, 2, 3, 5 and 7

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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mg/dL				
arithmetic mean (full range (min-max))	0.016 (-0.46 to 1.51)	0.003 (-0.47 to 0.39)		

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)[32]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: IU/L				
arithmetic mean (full range (min-max))	0.1 (-109 to 167)	1.1 (-229 to 78)		

Statistical analyses

No statistical analyses for this end point

Primary: Glomerular Filtration Rate (change from baseline)

End point title	Glomerular Filtration Rate (change from baseline)[33]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mL/min/1.73m2				
arithmetic mean (full range (min-max))	-0.2 (-32 to 5)	0 (-5 to 5)		

Statistical analyses

No statistical analyses for this end point

Primary: Glucose (change from baseline)

End point title	Glucose (change from baseline)[34]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mg/dL				
arithmetic mean (full range (min-max))	-1.3 (-215 to 175)	3.3 (-142 to 208)		

Statistical analyses

No statistical analyses for this end point

Primary: Magnesium (change from baseline)

End point title	Magnesium (change from baseline)[35]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mg/dL				
arithmetic mean (full range (min-max))	0 (-0.5 to 1)	-0.01 (-0.5 to 0.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Phosphate (change from baseline)

End point title	Phosphate (change from baseline)[36]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mg/dL				
arithmetic mean (full range (min-max))	-0.02 (-2 to 5.8)	-0.03 (-1.9 to 2.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Potassium (change from baseline)

End point title	Potassium (change from baseline)[37]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mEq/L				
arithmetic mean (full range (min-max))	0.02 (-1.6 to 1.7)	0.08 (-1.1 to 1.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Prolactin (change from baseline)

End point title	Prolactin (change from baseline)[38]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: ug/L				
arithmetic mean (full range (min-max))	1.88 (-149.1 to 175)	-2.25 (-88.9 to 74.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Protein (change from baseline)

End point title	Protein (change from baseline)[39]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: g/dL				
arithmetic mean (full range (min-max))	-0.05 (-2.1 to 1.2)	-0.04 (-1.7 to 1.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Sodium (change from baseline)

End point title	Sodium (change from baseline)[40]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mEq/L				
arithmetic mean (full range (min-max))	0.5 (-7 to 11)	0.6 (-7 to 10)		

Statistical analyses

No statistical analyses for this end point

Primary: Urate (change from baseline)

End point title	Urate (change from baseline)[41]

End point description:

End point type	Primary

End point timeframe:

These non-fasting laboratory tests will be performed on Days 28, 56, 112, and 182, 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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mg/dL				
arithmetic mean (full range (min-max))	0.05 (-4.8 to 4.9)	-0.04 (-4.8 to 3)		

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)[42]

End point description:

End point type	Primary

End point timeframe:

At all study visits (except Day 14 telephone call).

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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mmHg				
arithmetic mean (full range (min-max))	0.4 (-40 to 41)	0.2 (-31 to 32)		

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)[43]

End point description:

End point type	Primary

End point timeframe:

At all study visits (except Day 14 telephone call).

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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: mmHg				
arithmetic mean (full range (min-max))	0.1 (-32 to 42)	0.7 (-30 to 33)		

Statistical analyses

No statistical analyses for this end point

Primary: Pulse Rate (change from baseline)

End point title	Pulse Rate (change from baseline)[44]

End point description:

End point type	Primary

End point timeframe:

At all study visits (except Day 14 telephone call).

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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: beats/min				
arithmetic mean (full range (min-max))	2.3 (-33 to 46)	0.9 (-29 to 27)		

Statistical analyses

No statistical analyses for this end point

Primary: Respiratory Rate (change from baseline)

End point title	Respiratory Rate (change from baseline)[45]

End point description:

End point type	Primary

End point timeframe:

At all study visits (except Day 14 telephone call).

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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: breaths/min				
arithmetic mean (full range (min-max))	0.2 (-4 to 12)	-0.2 (-6 to 8)		

Statistical analyses

No statistical analyses for this end point

Primary: Temperature (change from baseline)

End point title	Temperature (change from baseline)[46]

End point description:

End point type	Primary

End point timeframe:

At all study visits (except Day 14 telephone call).

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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: celsius temperature				
arithmetic mean (full range (min-max))	0.02 (-1.3 to 1)	0.02 (-1.4 to 1.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Weight (change from baseline)

End point title	Weight (change from baseline)[47]

End point description:

End point type	Primary

End point timeframe:

At all study visits (except Day 14 telephone call).

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: This was a safety extension study, so there were no pre-defined statistical analysis.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	399		
Units: kilogram(s)				
arithmetic mean (full range (min-max))	-0.45 (-19.9 to 13.5)	-0.04 (-19.1 to 11.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: CGI-S severity scores (change from baseline)

End point title	CGI-S severity scores (change from baseline)

End point description:

End point type	Secondary

End point timeframe:

On Days 56, 112, and 182, or ET.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	421	388		
Units: n/a				
arithmetic mean (full range (min-max))	-0.1 (-2 to 2)	-0.1 (-2 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: CGI-C change scores (Day 182)

End point title	CGI-C change scores (Day 182)

End point description:

End point type	Secondary

End point timeframe:

On Days 56, 112, and 182, or ET.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	421	388		
Units: n/a				
arithmetic mean (full range (min-max))	3.1 (1 to 6)	3.1 (1 to 7)		

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)

End point description:

End point type	Other pre-specified

End point timeframe:

On Days 28, 56, 112, and 182, or ET.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	427	394		
Units: ng/ml				
arithmetic mean (full range (min-max))	1.59224 (0 to 5.06)	3.13547 (0 to 9.45)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Concentration of EVP-6124 N-Oxide Metabolite (Day 182)

End point description:

End point type	Other pre-specified

End point timeframe:

On Days 28, 56, 112, and 182, or ET.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	427	394		
Units: ng/ml				
arithmetic mean (full range (min-max))	0.17276 (0 to 0.778)	0.30632 (0 to 1.05)		

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)

End point description:

End point type	Other pre-specified

End point timeframe:

On Days 28, 56, 112, and 182, or ET.

End point values	EVP-6124, 1 mg	EVP-6124, 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	427	394		
Units: ng/ml				
arithmetic mean (full range (min-max))	0.22055 (0 to 0.678)	0.44114 (0 to 2.24)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	EVP-6124, 1 mg
Reporting group description:	
Subjects who received EVP-6124 during the previous study (EVP-6124-015 or EVP-6124-016) will remain on the same dose. Subjects who received placebo during the pivotal study (EVP-6124-015 or EVP-6124-016) will be randomized (1:1 ratio) to once daily EVP-6124 1 or 2 mg tablets for up to 26 weeks (Days 1-182).	
Reporting group title	EVP-6124, 2 mg
Reporting group description:	
Subjects who received EVP-6124 during the previous study (EVP-6124-015 or EVP-6124-016) will remain on the same dose. Subjects who received placebo during the pivotal study (EVP-6124-015 or EVP-6124-016) will be randomized (1:1 ratio) to once daily EVP-6124 1 or 2 mg tablets for up to 26 weeks (Days 1-182).	

Serious adverse events	EVP-6124, 1 mg	EVP-6124, 2 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 428 (2.80%)	20 / 399 (5.01%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Burns third degree			

subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Homicide			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	

Volvulus			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric decompensation			
subjects affected / exposed	7 / 428 (1.64%)	7 / 399 (1.75%)	
occurrences causally related to treatment / all	0 / 12	1 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance abuse			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 12	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	EVP-6124, 1 mg	EVP-6124, 2 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	164 / 428 (38.32%)	149 / 399 (37.34%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 428 (0.47%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Hyperaemia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 428 (0.47%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Fatigue			
subjects affected / exposed	2 / 428 (0.47%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Chest pain			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	

Non-cardiac chest pain			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Drug withdrawal syndrome			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Feeling jittery			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Hernia			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Inflammation			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Injection site swelling			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Malaise			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Oedema peripheral			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Pain			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Peripheral swelling			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Seasonal allergy			

subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Social circumstances			
Homicide			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 428 (0.47%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Amenorrhoea			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Erectile dysfunction			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Menstrual disorder			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 428 (0.93%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Rhinorrhoea			
subjects affected / exposed	1 / 428 (0.23%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Nasal congestion			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Oropharyngeal pain			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Allergic pharyngitis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Asthma			

subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Dyspnoea			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Epistaxis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Nasal polyps			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Nocturnal dyspnoea			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Oropharyngeal discomfort			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Productive cough			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Respiratory disorder			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Respiratory distress			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Rhinitis allergic			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Sneezing			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 428 (3.27%)	8 / 399 (2.01%)	
occurrences (all)	164	149	

Psychiatric decompensation			
subjects affected / exposed	8 / 428 (1.87%)	14 / 399 (3.51%)	
occurrences (all)	164	149	
Anxiety			
subjects affected / exposed	10 / 428 (2.34%)	5 / 399 (1.25%)	
occurrences (all)	164	149	
Depression			
subjects affected / exposed	5 / 428 (1.17%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Psychotic disorder			
subjects affected / exposed	3 / 428 (0.70%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Suicidal ideation			
subjects affected / exposed	3 / 428 (0.70%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Irritability			
subjects affected / exposed	2 / 428 (0.47%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Panic attack			
subjects affected / exposed	3 / 428 (0.70%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Initial insomnia			
subjects affected / exposed	2 / 428 (0.47%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Agitation			
subjects affected / exposed	2 / 428 (0.47%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Delusion			
subjects affected / exposed	2 / 428 (0.47%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Depressed mood			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Restlessness			
subjects affected / exposed	2 / 428 (0.47%)	0 / 399 (0.00%)	
occurrences (all)	164	149	

Abnormal dreams			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Affect lability			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Aggression			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Bruxism			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Hallucination			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Hallucination, auditory			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Hallucination, visual			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Homicidal ideation			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Middle insomnia			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Paranoia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Sleep disorder			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Sleep terror			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	

Stress			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Substance abuse			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Suicidal behaviour			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Tension			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Investigations			
Weight increased			
subjects affected / exposed	10 / 428 (2.34%)	7 / 399 (1.75%)	
occurrences (all)	164	149	
Weight decreased			
subjects affected / exposed	4 / 428 (0.93%)	6 / 399 (1.50%)	
occurrences (all)	164	149	
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 428 (1.17%)	4 / 399 (1.00%)	
occurrences (all)	164	149	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 428 (0.93%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Blood glucose increased			
subjects affected / exposed	1 / 428 (0.23%)	4 / 399 (1.00%)	
occurrences (all)	164	149	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 428 (0.47%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Urine leukocyte esterase positive			

subjects affected / exposed	2 / 428 (0.47%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
White blood cell count increased			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Blood bilirubin increased			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Blood creatinine increased			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Blood potassium decreased			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Blood pressure increased			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Neutrophil count increased			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
White blood cells urine positive			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 428 (0.47%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Laceration			

subjects affected / exposed	1 / 428 (0.23%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Sunburn			
subjects affected / exposed	3 / 428 (0.70%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Fall			
subjects affected / exposed	2 / 428 (0.47%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Multiple injuries			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Road traffic accident			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Skin abrasion			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Wound			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Arthropod bite			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Burns first degree			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Burns third degree			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Excoriation			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Intentional overdose			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Joint dislocation			

subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Ligament injury			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Ligament sprain			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Meniscus injury			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Nail injury			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Spinal fracture			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Toxicity to various agents			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Upper limb fracture			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Periorbital contusion			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Tachycardia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Nervous system disorders			
Headache			

subjects affected / exposed	24 / 428 (5.61%)	12 / 399 (3.01%)	
occurrences (all)	164	149	
Dizziness			
subjects affected / exposed	6 / 428 (1.40%)	4 / 399 (1.00%)	
occurrences (all)	164	149	
Tremor			
subjects affected / exposed	2 / 428 (0.47%)	4 / 399 (1.00%)	
occurrences (all)	164	149	
Somnolence			
subjects affected / exposed	3 / 428 (0.70%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Paraesthesia			
subjects affected / exposed	2 / 428 (0.47%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Akathisia			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Memory impairment			
subjects affected / exposed	2 / 428 (0.47%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Mental impairment			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Bradykinesia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Disturbance in attention			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Hypersomnia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Hypoaesthesia			

subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Intercostal neuralgia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Lethargy			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Restless legs syndrome			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Tension headache			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Iron deficiency anaemia			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Leukopenia			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Vertigo			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 428 (0.23%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Dry eye			

subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Iritis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Oculogyric crisis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Scleral hyperaemia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Vitreous floaters			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 428 (2.57%)	14 / 399 (3.51%)	
occurrences (all)	164	149	
Diarrhoea			
subjects affected / exposed	6 / 428 (1.40%)	9 / 399 (2.26%)	
occurrences (all)	164	149	
Nausea			
subjects affected / exposed	8 / 428 (1.87%)	3 / 399 (0.75%)	
occurrences (all)	164	149	
Toothache			
subjects affected / exposed	4 / 428 (0.93%)	4 / 399 (1.00%)	
occurrences (all)	164	149	
Abdominal pain upper			
subjects affected / exposed	5 / 428 (1.17%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Dyspepsia			
subjects affected / exposed	2 / 428 (0.47%)	4 / 399 (1.00%)	
occurrences (all)	164	149	
Abdominal pain			
subjects affected / exposed	1 / 428 (0.23%)	3 / 399 (0.75%)	
occurrences (all)	164	149	

Vomiting			
subjects affected / exposed	3 / 428 (0.70%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Dry mouth			
subjects affected / exposed	2 / 428 (0.47%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Food poisoning			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Abdominal hernia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Dental caries			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Dysphagia			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Faeces hard			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Faeces soft			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Haemorrhoids			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Large intestine polyp			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Lip blister			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Lip pain			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	

Salivary hypersecretion			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Tooth impacted			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Volvulus			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Alopecia			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Eczema			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Hyperhidrosis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Rash			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Rash papular			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Skin exfoliation			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Swelling face			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Urticaria			

subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Renal and urinary disorders			
Hypertonic bladder			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Pollakiuria			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Bladder disorder			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Enuresis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Haematuria			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Urine flow decreased			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Endocrine disorders			
Hyperprolactinaemia			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Goitre			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Hypothyroidism			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	2 / 428 (0.47%)	6 / 399 (1.50%)	
occurrences (all)	164	149	
Arthralgia			
subjects affected / exposed	2 / 428 (0.47%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Muscle spasms			
subjects affected / exposed	2 / 428 (0.47%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Pain in extremity			
subjects affected / exposed	1 / 428 (0.23%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Arthritis			
subjects affected / exposed	2 / 428 (0.47%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Myalgia			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Coccydynia			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Muscle rigidity			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Musculoskeletal pain			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Periarthritis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 428 (3.04%)	20 / 399 (5.01%)	
occurrences (all)	164	149	
Influenza			
subjects affected / exposed	3 / 428 (0.70%)	7 / 399 (1.75%)	
occurrences (all)	164	149	
Upper respiratory tract infection			
subjects affected / exposed	8 / 428 (1.87%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Urinary tract infection			
subjects affected / exposed	7 / 428 (1.64%)	3 / 399 (0.75%)	
occurrences (all)	164	149	
Bronchitis			
subjects affected / exposed	4 / 428 (0.93%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Ear infection			
subjects affected / exposed	2 / 428 (0.47%)	3 / 399 (0.75%)	
occurrences (all)	164	149	
Pharyngitis			
subjects affected / exposed	2 / 428 (0.47%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Gastroenteritis			
subjects affected / exposed	1 / 428 (0.23%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Abscess limb			
subjects affected / exposed	2 / 428 (0.47%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Cellulitis			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Gastroenteritis viral			
subjects affected / exposed	2 / 428 (0.47%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Pneumonia			

subjects affected / exposed	2 / 428 (0.47%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Respiratory tract infection			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Sinusitis			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Appendicitis			
subjects affected / exposed	0 / 428 (0.00%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Conjunctivitis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Diverticulitis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Folliculitis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Furuncle			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Gingivitis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Helicobacter gastritis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Hordeolum			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Infected bites			

subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Laryngitis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Otitis externa			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Otitis media			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Respiratory tract infection viral			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Skin candida			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Subcutaneous abscess			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Tonsillitis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Tooth abscess			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Tooth infection			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Varicella			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	2 / 428 (0.47%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Increased appetite			
subjects affected / exposed	1 / 428 (0.23%)	2 / 399 (0.50%)	
occurrences (all)	164	149	
Vitamin D deficiency			
subjects affected / exposed	1 / 428 (0.23%)	1 / 399 (0.25%)	
occurrences (all)	164	149	
Decreased appetite			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Food craving			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Gout			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Hypercholesterolaemia			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Hyperlipidaemia			
subjects affected / exposed	1 / 428 (0.23%)	0 / 399 (0.00%)	
occurrences (all)	164	149	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 428 (0.00%)	1 / 399 (0.25%)	
occurrences (all)	164	149	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2013	Protocol Amendment 1 (08 March 2013)
02 August 2013	Protocol Amendment 2 (02 August 2013)
26 August 2014	Protocol Amendment 2.1 (26 August 2014)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported