Clinical trial results:
A randomized, double-blind, placebo-controlled, parallel-group study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple oral doses of CNP520 in healthy elderly subjects

Summary

EudraCT number	2013-005576-18
Trial protocol	NL DE BE GB
Global end of trial date	11 March 2016

Results information

Result version number	v1
This version publication date	25 March 2017
First version publication date	25 March 2017

Trial information

Trial identification

Sponsor protocol code	CCNP520X2102

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 61324 1111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 61324 1111,

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	11 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and tolerability of multiple, once-daily oral doses of CNP520 over 13 weeks in healthy elderly subjects.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	10 August 2015
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	United States: 55
Country: Number of subjects enrolled	Netherlands: 29
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	124
EEA total number of subjects	69

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)	52
From 65 to 84 years	72
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized in a 1:1:1:1:1 ratio to 5 treatment groups: placebo, CNP520 2 mg, CNP520 10 mg, CNP520 35 mg and CNP520 85 mg.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo to CNP520 was taken once daily (qd) orally for 13 weeks.

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

Dosage and administration details:

Matching placebo qd orally (2 capsules of placebo)

Arm title	CNP520 2 mg

Arm description:

CNP520 2 mg was taken qd orally for 13 weeks.

Arm type	Experimental
Investigational medicinal product name	CNP520
Investigational medicinal product code	CNP520
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CNP520 2 mg qd (2 capsules of 1 mg CNP520)

Arm title	CNP520 10 mg

Arm description:

CNP520 10 mg was taken qd orally for 13 weeks.

Arm type	Experimental
Investigational medicinal product name	CNP520
Investigational medicinal product code	CNP520
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details: CNP520 10 mg qd (1 capsule of CNP520 10 mg and 1 capsule of placebo)	

Arm title	CNP520 35 mg
Arm description: CNP520 35 mg was taken qd orally for 13 weeks.	
Arm type	Experimental
Investigational medicinal product name	CNP520
Investigational medicinal product code	CNP520
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: CNP520 35 mg qd (1 capsule of 25 mg CNP520 and 1 capsule of CNP520 10 mg)	

Arm title	CNP520 85 mg
Arm description: CNP520 85 mg was taken qd orally for 13 weeks.	
Arm type	Experimental
Investigational medicinal product name	CNP520
Investigational medicinal product code	CNP520
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: CNP520 85 mg qd (1 capsule of CNP520 75 mg and 1 capsule of CNP520 10 mg)	

Number of subjects in period 1	Placebo	CNP520 2 mg	CNP520 10 mg
Started	24	25	25
Safety analysis set	24	25	25
Pharmacokinetic analysis set	0 [1]	25	25
Pharmacodynamic analysis set	24	24	25
Completed	22	23	23
Not completed	2	2	2
Consent withdrawn by subject	1	2	1
Physician decision	-	-	-
Adverse event, non-fatal	1	-	1

Number of subjects in period 1	CNP520 35 mg	CNP520 85 mg
Started	26	24
Safety analysis set	26	24
Pharmacokinetic analysis set	26	24

Pharmacodynamic analysis set	25	24
Completed	25	20
Not completed	1	4
Consent withdrawn by subject	-	1
Physician decision	-	1
Adverse event, non-fatal	1	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Pharmacokinetic analysis does not apply to the placebo group.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to CNP520 was taken once daily (qd) orally for 13 weeks.	
Reporting group title	CNP520 2 mg
Reporting group description:	
CNP520 2 mg was taken qd orally for 13 weeks.	
Reporting group title	CNP520 10 mg
Reporting group description:	
CNP520 10 mg was taken qd orally for 13 weeks.	
Reporting group title	CNP520 35 mg
Reporting group description:	
CNP520 35 mg was taken qd orally for 13 weeks.	
Reporting group title	CNP520 85 mg
Reporting group description:	
CNP520 85 mg was taken qd orally for 13 weeks.	

Reporting group values	Placebo	CNP520 2 mg	CNP520 10 mg
Number of subjects	24	25	25
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	12	8
From 65-84 years	13	13	17
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	66.6	65.4	66.8
standard deviation	± 5.3	± 4.6	± 5.1
Gender categorical Units: Subjects			
Female	12	16	13
Male	12	9	12

Reporting group values	CNP520 35 mg	CNP520 85 mg	Total
Number of subjects	26	24	124
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0

Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	11	52
From 65-84 years	16	13	72
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	66.1	66.5	
standard deviation	± 4.6	± 5.2	-
Gender categorical			
Units: Subjects			
Female	11	9	61
Male	15	15	63

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching placebo to CNP520 was taken once daily (qd) orally for 13 weeks.	
Reporting group title	CNP520 2 mg
Reporting group description:	
CNP520 2 mg was taken qd orally for 13 weeks.	
Reporting group title	CNP520 10 mg
Reporting group description:	
CNP520 10 mg was taken qd orally for 13 weeks.	
Reporting group title	CNP520 35 mg
Reporting group description:	
CNP520 35 mg was taken qd orally for 13 weeks.	
Reporting group title	CNP520 85 mg
Reporting group description:	
CNP520 85 mg was taken qd orally for 13 weeks.	

Primary: Number of participants with non-serious and serious adverse events (AEs) and deaths

End point title	Number of participants with non-serious and serious adverse events (AEs) and deaths[1]
End point description:	
Safety monitoring was conducted throughout the study.	
End point type	Primary
End point timeframe:	
13 weeks	

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 analysis does not apply to this end point.

End point values	Placebo	CNP520 2 mg	CNP520 10 mg	CNP520 35 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	25	25	26
Units: Participants				
Non-serious AEs	18	19	22	20
Serious AEs	0	0	0	1
Deaths	0	0	0	0

End point values	CNP520 85 mg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Participants				
Non-serious AEs	18			

Serious AEs	0			
Deaths	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in of amyloid beta (Aβ) 1-38, Aβ 1-40 and Aβ 1-42 cerebospinal fluid (CSF) concentrations

End point title	Change from baseline in of amyloid beta (Aβ) 1-38, Aβ 1-40 and Aβ 1-42 cerebospinal fluid (CSF) concentrations

End point description:

CSF samples were collected by lumbar puncture for assessment. The pharmacodynamics (PD) analysis set was analyzed. The PD set included only randomized participants who had available PD data and no protocol deviations with relevant impact on PD data.

End point type	Secondary

End point timeframe:

Day 92

End point values	Placebo	CNP520 2 mg	CNP520 10 mg	CNP520 35 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	22	21	23
Units: Percentage				
arithmetic mean (standard deviation)				
Aβ 1-38	-2.34 (± 6.969)	-20.55 (± 10.475)	-62.48 (± 6.202)	-82.93 (± 4.378)
Aβ 1-40	-2.64 (± 6.598)	-22.64 (± 9.937)	-62.89 (± 6.485)	-83.16 (± 4.227)
Aβ 1-42	-2.58 (± 5.189)	-23.93 (± 8.987)	-64.28 (± 6.086)	-82.35 (± 5.474)

End point values	CNP520 85 mg			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage				
arithmetic mean (standard deviation)				
Aβ 1-38	-89.5 (± 1.676)			
Aβ 1-40	-90.69 (± 1.651)			
Aβ 1-42	-89.68 (± 2.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma PK parameter: Cmax

End point title	Summary of plasma PK parameter: Cmax[2]

End point description:

Cmax = the observed maximum plasma concentration following drug administration. Blood samples were collected to assess Cmax. The PK analysis set was used for the analysis. For a given time point, only those participants from the PK analysis set, who had PK data and had no protocol deviations with relevant impact on PK data, were analyzed for that time point.

End point type	Secondary

End point timeframe:

Days 1, 91

Notes:

[2] - 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 placebo group does not apply to this end point.

End point values	CNP520 2 mg	CNP520 10 mg	CNP520 35 mg	CNP520 85 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	26	24
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=25,25,26,24)	4.76 (± 2.92)	21.3 (± 6.67)	75.6 (± 23.4)	163 (± 47.4)
Day 91 (=23,22,24,20)	16.6 (± 5.51)	81 (± 29.2)	237 (± 65.7)	602 (± 150)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma PK parameter: AUCtau

End point title	Summary of plasma PK parameter: AUCtau[3]

End point description:

AUCtau = the area under the plasma concentration-time curve from zero to the end of the dosing interval tau. Blood samples were collected to assess AUCtau. The PK analysis set was used for the analysis. For a given time point, only those participants from the PK analysis set, who had PK data and had no protocol deviations with relevant impact on PK data, were analyzed for that time point.

End point type	Secondary

End point timeframe:

Days 1 and 91

Notes:

[3] - 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 placebo group does not apply to this end point.

End point values	CNP520 2 mg	CNP520 10 mg	CNP520 35 mg	CNP520 85 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	26	24
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=25,25,26,24)	67.1 (± 60.7)	278 (± 65.7)	966 (± 214)	2300 (± 479)
Day 91 (n=23,26,24,20)	313 (± 117)	1500 (± 476)	4450 (± 1090)	11200 (± 3320)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma PK parameter: Tmax

End point title	Summary of plasma PK parameter: Tmax[4]

End point description:

Tmax = the time to reach the maximum concentration after drug administration. Blood samples were collected to assess Tmax. The PK analysis set was used for the analysis. For a given time point, only those participants from the PK analysis set, who had PK data and had no protocol deviations with relevant impact on PK data, were analyzed for that time point.

End point type	Secondary

End point timeframe:

Days 1 and 91

Notes:

[4] - 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 placebo group does not apply to this end point.

End point values	CNP520 2 mg	CNP520 10 mg	CNP520 35 mg	CNP520 85 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	26	24
Units: hour				
median (full range (min-max))				
Day 1 (n=25,25,26,24)	2.5 (2.45 to 9)	2.5 (2.5 to 6.02)	2.5 (2.48 to 9)	2.5 (2.42 to 12)
Day 91 (n=23,26,24,20)	2.5 (0 to 12.1)	2.5 (0 to 12.5)	2.5 (0 to 12)	2.5 (0 to 12)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma PK parameter: Tlag

End point title	Summary of plasma PK parameter: Tlag[5]

End point description:

Tlag = time delay between drug administration and first observed concentration above the lower limit of quantification (LOQ) in plasma . Blood samples were collected to assess Tlag. The PK analysis set was used for the analysis. For a given time point, only those participants from the PK analysis set, who had PK data and had no protocol deviations with relevant impact on PK data, were analyzed for that time point.

End point type	Secondary

End point timeframe:

Days 1 and 91

Notes:

[5] - 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 placebo group does not apply to this end point.

End point values	CNP520 2 mg	CNP520 10 mg	CNP520 35 mg	CNP520 85 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	26	24
Units: hour				
median (full range (min-max))				
Day 1 (n=25,25,26,24)	0.5 (0 to 0.567)	0.5 (0 to 2.5)	0.5 (0 to 0.55)	0 (0 to 2.5)
Day 91 (n=23,22,24,20)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma PK parameter: T1/2

End point title	Summary of plasma PK parameter: T1/2[6]

End point description:

T1/2 = the terminal elimination half-life. Blood samples were collected to assess T/12. The PK analysis set was used for the analysis. Only those participants from the PK analysis set, who had PK data and had no protocol deviations with relevant impact on PK data, were analyzed.

End point type	Secondary

End point timeframe:

Day 91

Notes:

[6] - 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 placebo group does not apply to this end point.

End point values	CNP520 2 mg	CNP520 10 mg	CNP520 35 mg	CNP520 85 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	22	24	20
Units: hour				
arithmetic mean (standard deviation)	150 (± 52.2)	155 (± 40.9)	155 (± 33.9)	160 (± 22)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of PK parameter: CLss/F

End point title	Summary of PK parameter: CLss/F[7]

End point description:

CLss/F = the apparent systemic clearance from plasma observed during a dosing interval at steady state following extravascular administration. Blood samples were collected to assess CLss/F. The PK analysis set was used for the analysis. Only those participants from the PK analysis set, who had PK data and had no protocol deviations with relevant impact on PK data, were analyzed.

End point type	Secondary

End point timeframe:

Day 91

Notes:

[7] - 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 placebo group does not apply to this end point.

End point values	CNP520 2 mg	CNP520 10 mg	CNP520 35 mg	CNP520 85 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	22	24	20
Units: mL/h				
arithmetic mean (standard deviation)	7260 (± 2620)	7380 (± 2480)	8460 (± 2790)	8220 (± 2270)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma PK parameter: Racc

End point title	Summary of plasma PK parameter: Racc[8]

End point description:

Racc = the accumulation ratio . Blood samples were collected to assess Racc. The PK analysis set was used for the analysis. Only those participants from the PK analysis set, who had PK data and had no protocol deviations with relevant impact on PK data, were analyzed.

End point type	Secondary

End point timeframe:

Day 91

Notes:

[8] - 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 placebo group does not apply to this end point.

End point values	CNP520 2 mg	CNP520 10 mg	CNP520 35 mg	CNP520 85 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	22	24	20
Units: ratio				
arithmetic mean (standard deviation)	5.86 (± 2.25)	5.33 (± 1.05)	4.75 (± 1.16)	5.02 (± 1.47)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of CSF PK concentrations

End point title	Summary of CSF PK concentrations[9]

End point description:

CSF samples were collected by lumbar puncture for assessment. The PK analysis set was used for the analysis. For a given time point, only those participants from the PK analysis set, who had PK data and had no protocol deviations with relevant impact on PK data, were analyzed for that time point.

End point type	Secondary

End point timeframe:

Days 1, 14, 28, 42, 56, 70 and 91

Notes:

[9] - 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 placebo group does not apply to this end point.

End point values	CNP520 2 mg	CNP520 10 mg	CNP520 35 mg	CNP520 85 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	26	24
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=24,25,26,24)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Day 14 (n=3,4,4,4)	0.116 (± 0.103)	1.07 (± 0.225)	3.82 (± 0.868)	8.13 (± 2.7)
Day 28 (n=5,2,7,5)	0.303 (± 0.0731)	1.48 (± 0.106)	4.48 (± 1.02)	12 (± 4.12)
Day 42 (n=3,6,5,5)	0.314 (± 0.0715)	1.52 (± 0.6)	4 (± 1.21)	7.47 (± 1.57)
Day 56 (n=5,5,2,4)	0.291 (± 0.0605)	1.28 (± 0.177)	5.03 (± 2.69)	8.04 (± 5.69)
Day 70 (n=6,5,6,4)	0.231 (± 0.149)	1.04 (± 0.212)	4.62 (± 0.753)	8.71 (± 0.71)
Day 91 (n=23,21,24,20)	0.305 (± 0.099)	1.44 (± 0.431)	4.52 (± 0.946)	10.4 (± 3.26)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	CNP520 2mg
Reporting group description:	
CNP520 2mg	
Reporting group title	CNP520 10mg
Reporting group description:	
CNP520 10mg	
Reporting group title	CNP520 35mg
Reporting group description:	
CNP520 35mg	
Reporting group title	CNP520 85mg
Reporting group description:	
CNP520 85mg	

Serious adverse events	Placebo	CNP520 2mg	CNP520 10mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	CNP520 35mg	CNP520 85mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	

number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	CNP520 2mg	CNP520 10mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 24 (75.00%)	19 / 25 (76.00%)	22 / 25 (88.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Seborrhoeic keratosis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	3 / 24 (12.50%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	5	0	0
Feeling cold			

subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Puncture site pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Vessel puncture site haemorrhage			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	2
Vessel puncture site pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Vessel puncture site swelling			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Immune system disorders			
Allergy to chemicals			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Erectile dysfunction			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Pruritus genital			

subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 24 (4.17%)	2 / 25 (8.00%)	3 / 25 (12.00%)
occurrences (all)	1	2	4
Dysphonia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Dyspnoea			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Hiccups			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	2 / 24 (8.33%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	2	0	1
Oropharyngeal pain			
subjects affected / exposed	4 / 24 (16.67%)	2 / 25 (8.00%)	2 / 25 (8.00%)
occurrences (all)	4	2	2
Productive cough			
subjects affected / exposed	1 / 24 (4.17%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Rhinorrhoea			
subjects affected / exposed	2 / 24 (8.33%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	2	0	2
Sinus congestion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Throat irritation			

subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	0	1	2
Affective disorder			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Libido decreased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Nightmare			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Obsessive thoughts			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Investigations			
Amylase increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Blood bilirubin increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 24 (0.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Blood triglycerides increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Weight decreased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Ear abrasion			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Foreign body in eye			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Joint dislocation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Ligament sprain			

subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Post lumbar puncture syndrome			
subjects affected / exposed	8 / 24 (33.33%)	2 / 25 (8.00%)	1 / 25 (4.00%)
occurrences (all)	9	3	1
Post procedural discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Post procedural haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Procedural complication			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Procedural dizziness			
subjects affected / exposed	2 / 24 (8.33%)	0 / 25 (0.00%)	3 / 25 (12.00%)
occurrences (all)	3	0	3
Procedural nausea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	1 / 24 (4.17%)	3 / 25 (12.00%)	4 / 25 (16.00%)
occurrences (all)	1	4	4
Scratch			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Thermal burn			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Traumatic lumbar puncture			

subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Wound complication			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Balance disorder			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Cognitive disorder			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	3 / 24 (12.50%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	3	0	7
Dizziness postural			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Dysarthria			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Head discomfort			
subjects affected / exposed	1 / 24 (4.17%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	1	1	1
Headache			
subjects affected / exposed	10 / 24 (41.67%)	11 / 25 (44.00%)	5 / 25 (20.00%)
occurrences (all)	16	16	7
Lethargy			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0

Neuropathy peripheral			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Sedation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Sinus headache			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Somnolence			
subjects affected / exposed	1 / 24 (4.17%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Syncope			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Tension headache			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Visual field defect			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Eustachian tube dysfunction			

subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Eye disorders			
Asthenopia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Eye irritation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	4
Eye pruritus			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Lacrimation increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Ocular hyperaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	1 / 24 (4.17%)	1 / 25 (4.00%)	2 / 25 (8.00%)
occurrences (all)	1	1	5
Visual impairment			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal distension			

subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	2 / 24 (8.33%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	2	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	5 / 24 (20.83%)	1 / 25 (4.00%)	3 / 25 (12.00%)
occurrences (all)	8	1	5
Dry mouth			
subjects affected / exposed	1 / 24 (4.17%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Dyspepsia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	2 / 25 (8.00%)
occurrences (all)	0	1	2
Eructation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Faeces hard			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Faeces soft			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	1 / 24 (4.17%)	1 / 25 (4.00%)	3 / 25 (12.00%)
occurrences (all)	1	1	4
Frequent bowel movements			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 24 (8.33%)	2 / 25 (8.00%)	3 / 25 (12.00%)
occurrences (all)	3	2	3
Toothache			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	2
Vomiting			
subjects affected / exposed	1 / 24 (4.17%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	2	2	0
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Ecchymosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 24 (0.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Pruritus			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	0	3

Pruritus generalised			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	2 / 25 (8.00%)
occurrences (all)	0	1	4
Psoriasis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Rash papular			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Polyuria			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 24 (4.17%)	2 / 25 (8.00%)	3 / 25 (12.00%)
occurrences (all)	1	2	3
Back pain			
subjects affected / exposed	6 / 24 (25.00%)	2 / 25 (8.00%)	2 / 25 (8.00%)
occurrences (all)	9	2	2
Joint stiffness			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Joint swelling			

subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Muscle tightness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 24 (0.00%)	2 / 25 (8.00%)	1 / 25 (4.00%)
occurrences (all)	0	2	1
Musculoskeletal stiffness			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
Neck pain			
subjects affected / exposed	1 / 24 (4.17%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	1	2	0
Pain in extremity			
subjects affected / exposed	2 / 24 (8.33%)	2 / 25 (8.00%)	1 / 25 (4.00%)
occurrences (all)	2	2	1
Plantar fasciitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1

Abscess jaw			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	4 / 24 (16.67%)	2 / 25 (8.00%)	5 / 25 (20.00%)
occurrences (all)	6	2	5
Oral herpes			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Tinea pedis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 24 (8.33%)	1 / 25 (4.00%)	2 / 25 (8.00%)
occurrences (all)	3	1	3
Urinary tract infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Increased appetite			

subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	CNP520 35mg	CNP520 85mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 26 (76.92%)	18 / 24 (75.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Seborrhoeic keratosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	2 / 26 (7.69%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Feeling cold			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Injection site pain			
subjects affected / exposed	1 / 26 (3.85%)	2 / 24 (8.33%)	
occurrences (all)	1	2	

Pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Puncture site pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Vessel puncture site haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Vessel puncture site pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Vessel puncture site swelling			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Allergy to chemicals			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Erectile dysfunction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Pruritus genital			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 26 (11.54%)	3 / 24 (12.50%)	
occurrences (all)	4	3	
Dysphonia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Dyspnoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Epistaxis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Hiccups			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Nasal congestion			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 26 (7.69%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Productive cough			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	1	2	
Sinus congestion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Throat irritation			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Affective disorder			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Confusional state			

subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Irritability			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Libido decreased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Nightmare			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Obsessive thoughts			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Investigations			
Amylase increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Blood cholesterol increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Blood triglycerides increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Lipase increased			

subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Contusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Ear abrasion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Foreign body in eye			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Joint dislocation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Laceration			
subjects affected / exposed	2 / 26 (7.69%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Ligament sprain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Limb injury			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Post lumbar puncture syndrome			
subjects affected / exposed	3 / 26 (11.54%)	3 / 24 (12.50%)	
occurrences (all)	3	3	
Post procedural discomfort			

subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Procedural complication			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Procedural dizziness			
subjects affected / exposed	2 / 26 (7.69%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Procedural nausea			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Procedural pain			
subjects affected / exposed	2 / 26 (7.69%)	3 / 24 (12.50%)	
occurrences (all)	3	3	
Scratch			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Skin abrasion			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Traumatic lumbar puncture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Wound complication			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	

Balance disorder			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Cognitive disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dizziness postural			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Dysarthria			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Head discomfort			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	5 / 26 (19.23%)	5 / 24 (20.83%)	
occurrences (all)	11	11	
Lethargy			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Sedation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	

Sinus headache			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	2 / 26 (7.69%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Syncope			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Tension headache			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Visual field defect			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Eustachian tube dysfunction			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Asthenopia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Dry eye			

subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Eye irritation			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Eye pruritus			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Lacrimation increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Ocular hyperaemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	2 / 26 (7.69%)	1 / 24 (4.17%)	
occurrences (all)	2	2	

Diarrhoea			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Dry mouth			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Eructation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Faeces hard			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Faeces soft			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Flatulence			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Frequent bowel movements			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Glossodynia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 26 (7.69%)	2 / 24 (8.33%)	
occurrences (all)	3	3	
Toothache			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	3	2	

Vomiting			
subjects affected / exposed	2 / 26 (7.69%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Dermatitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Dermatitis contact			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Dry skin			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Ecchymosis			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Erythema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Pruritus generalised			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Psoriasis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Rash papular			

subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Pollakiuria			
subjects affected / exposed	2 / 26 (7.69%)	1 / 24 (4.17%)	
occurrences (all)	4	1	
Polyuria			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 26 (11.54%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Back pain			
subjects affected / exposed	3 / 26 (11.54%)	4 / 24 (16.67%)	
occurrences (all)	3	5	
Joint stiffness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Joint swelling			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Muscle tightness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			

subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal discomfort			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	2 / 26 (7.69%)	1 / 24 (4.17%)	
occurrences (all)	2	4	
Neck pain			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Pain in extremity			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Plantar fasciitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Abscess jaw			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Hordeolum			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	

Nasopharyngitis			
subjects affected / exposed	4 / 26 (15.38%)	1 / 24 (4.17%)	
occurrences (all)	5	1	
Oral herpes			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Tinea pedis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Increased appetite			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 August 2015	Amendment 1 was issued approximately 4 months after original protocol to address Medicines and Healthcare Products Regulatory Agency (MHRA) requests and at the time of the amendment finalization only 2 subjects were screened and none randomized. Study drug discontinuation criteria were modified such that those listed under the discretion of the Investigator were changed to mandatory individual discontinuation criteria. This amendment introduced the following changes: Section 7.1 Discontinuation of study treatment: The following 4 discontinuation criteria that were under the discretion of the Investigator were changed to mandatory individual discontinuation criteria: • Suspected event of drug-induced renal toxicity based on clinical signs and/or laboratory parameters including an increase of serum creatinine by ≥25% compared to baseline • Major non-compliance with study requirements including drug intake • Indication for increased suicidal risk (as determined by C-SSRS assessments) • QTcF prolongation of >60 msec compared to baseline or QTcF >500 msec As a consequence of this change, the following mandatory discontinuation criterion became redundant and had therefore been removed: • QTcF prolongation of >60 msec compared to baseline in combination with QTcF >500 msec
13 October 2015	Amendment 2 was made to address comments raised by health authorities and ethics committees in the course of protocol review and IND application. The amendment was issued (when 99 subjects were screened and 44 of these were randomized) and introduced the following key changes: •Addition of an exclusion criterion regarding signs or symptoms of raised intracranial blood pressure and thrombocytopenia. •In addition, it was requested by the UK Ethics committee that a minimum of 24 h stay was required after each lumbar puncture. In the original protocol, a 24 h stay was already included at visits including the first and third lumbar puncture, due to other assessments (eg, PK time course, safety observation after first dosage administration). The Amendment 2 clarified that if required, a 24 h stay post the second lumbar puncture could occur based on local requirements.
08 December 2015	Amendment 3 was made to address FDA feedback received in context of a pre-IND meeting. This was issued when all 125 subjects were screened and all were randomized. Therefore, an additional Part II was added to this trial primarily in order to assess the PD effects of CNP520 in hetero- and homozygous ApoE4 carriers compared to homozygous ApoE3 subjects as reference group. It introduced the following changes: •An additional Part II was added to this trial primarily in order to assess the PD effects of CNP520 in hetero- and homozygous ApoE4 carriers compared to homozygous ApoE3 subjects as reference group. This Part II was planned to run independently of the core study that would be referred to as Part I. There were no data from Part I that would be required to start Part II or vice versa. However, the Part II of the study was not implemented. • In addition, this amendment clarified that blood cotinine was required only at screening. In all previous protocol versions there was conflicting information.

11 March 2016	Amendment 4 was made to remove the group of heterozygous ApoE4 carriers in Part II of this clinical study following exploratory genetic analysis of data from CNP520X2101 which indicated no relevant difference of the PD effects of CNP520 in heterozygous ApoE4 carriers compared to wild-type subjects. This amendment was issued when all subjects were screened, randomized and completed the trial and introduced the following changes: •As exploratory genetic analysis of data from the FIH study CCNP520X2101 indicated no relevant difference of the PD effects of CNP520 in heterozygous ApoE4 carriers compared to wild-type subjects, this amendment was made to remove the group of heterozygous ApoE4 carriers in Part II of this clinical study. •In addition, based on preliminary data from the FIH, an increase in plasma 4β-hydroxy cholesterol ratio post-treatment/baseline was observed in the 2-week CNP520 multiple dose part indicating induction of CYP3A4. Measurement of plasma 4β-OH cholesterol was added in this study to evaluate if CNP520 induces CYP3A4 after three months CNP520 treatment at dose levels ranging from 2 mg once daily to 85 mg qd, and an exploratory objective was added to Part I of this study. • Finally, in order to appropriately analyze Part I data and properly design future clinical trials, the protocol clarified that an interim analysis of Part I could be conducted. This interim analysis would take place once all subjects of Part I had completed the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported