Clinical trial results:
A randomized, double-blind, placebo-controlled, two-cohort parallel group study to evaluate the efficacy of CAD106 and CNP520 in participants at risk for the onset of clinical symptoms of Alzheimer's disease

Summary

EudraCT number	2015-002715-15
Trial protocol	BE ES FI NL DE
Global end of trial date	30 April 2020

Results information

Result version number	v1 (current)
This version publication date	14 May 2021
First version publication date	14 May 2021

Trial information

Trial identification

Sponsor protocol code	CAPI015A2201J

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02565511
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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	30 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The first primary objective of the trial was to demonstrate the effects of CAD106 and CNP520 vs. respective placebo on Time-to-event (TTE), with event defined as a diagnosis of MCI due to AD or dementia due to AD, whichever occured first during the course of the study. The second primary objective was to demonstrate the effects of CAD106 and CNP520 vs. respective placebo on cognition as measured by the change from Baseline to Month 60 in the APCC test.

The study was terminated due to unexpected changes in cognitive function, brain volume loss, and body weight loss. Cohort II (CNP520) treatment was stopped and evaluated through an off-treatment follow-up period. After the decision to terminate Cohort II of the study (CNP520), treatment with CAD106 (Cohort I) was also terminated.

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 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	United Kingdom: 47
Country: Number of subjects enrolled	United States: 346
Worldwide total number of subjects	477
EEA total number of subjects	55

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)	158
From 65 to 84 years	319
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

713 participants were screened. Three subjects were mis-randomized and not included in the subject disposition for Cohort II (2 in CNP520 and 1 in CNP520 placebo).

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, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort I (CI) CAD106

Arm description:

CAD106 (450 µg) + Alum (450 µg) intra-muscular injection at Weeks 1, 7, 13 and every 13 weeks thereafter

Arm type	Experimental
Investigational medicinal product name	CAD106
Investigational medicinal product code	CAD106
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants will be given i.m. injections at Weeks 1, 7, 13 and
quarterly i.m. injections (every 13 weeks) thereafter, until the last injection 3 month prior to completion of the Treatment Epoch.

Arm title	Cohort I (CI) CAD106 Placebo

Arm description:

Placebo to CAD106 + Alum (450 µg) intra-muscular injection at Weeks 1, 7, 13 and every 13 weeks thereafter

Arm type	Placebo
Investigational medicinal product name	CAD106 Placebo
Investigational medicinal product code	CAD106
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants will be given i.m. injections at Weeks 1, 7, 13 and
quarterly i.m. injections (every 13 weeks) thereafter, until the last injection 3 month prior to completion of the Treatment Epoch.

Arm title	Cohort II (CII) CNP520

Arm description:

CNP520 (50 mg) capsules taken once daily orally

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 50 mg capsule taken orally once a day for the duration of the Treatment Epoch

Arm title	Cohort II (CII) CNP520 Placebo

Arm description:

Placebo to CNP520 capsules taken once daily orally

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

Dosage and administration details:

CNP520 Placebo capsule taken orally once a day for the duration of the Treatment Epoch

Number of subjects in period 1	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520
Started	42	23	249
Completed	0	0	0
Not completed	42	23	249
Consent withdrawn by subject	3	-	12
Physician decision	-	-	-
Study terminated by Sponsor	35	22	233
Adverse event, non-fatal	-	-	1
Protocol deviation	-	-	3
Lost to follow-up	4	1	-

Number of subjects in period 1	Cohort II (CII) CNP520 Placebo
Started	163
Completed	0
Not completed	163
Consent withdrawn by subject	5
Physician decision	1
Study terminated by Sponsor	155
Adverse event, non-fatal	1
Protocol deviation	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort I (CI) CAD106
Reporting group description:	
CAD106 (450 µg) + Alum (450 µg) intra-muscular injection at Weeks 1, 7, 13 and every 13 weeks thereafter	
Reporting group title	Cohort I (CI) CAD106 Placebo
Reporting group description:	
Placebo to CAD106 + Alum (450 µg) intra-muscular injection at Weeks 1, 7, 13 and every 13 weeks thereafter	
Reporting group title	Cohort II (CII) CNP520
Reporting group description:	
CNP520 (50 mg) capsules taken once daily orally	
Reporting group title	Cohort II (CII) CNP520 Placebo
Reporting group description:	
Placebo to CNP520 capsules taken once daily orally	

Reporting group values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520
Number of subjects	42	23	249
Age Categorical Units: participants			
<=64 years	20	9	77
65-69 years	18	7	116
>70 years	4	7	56
Sex: Female, Male Units: participants			
Female	27	17	129
Male	15	6	120
Race/Ethnicity, Customized Units: Subjects			
Caucasian	41	22	241
Black	1	1	1
Asian	0	0	4
Pacific Islander	0	0	1
Other	0	0	1
Unknown	0	0	1
API Preclinical Composite Cognitive Battery (APCC)			
APCC (API Preclinical Compo site Cognitive Battery) is a composite score derived from RBANS (Repeatable Battery for Assessment of Neurological Status), MMSE (Mini-Mental State Examination) and the Raven's Progressive Matrices; scores are 0-100 and higher scores indicate better cognitive performance.			
Units: Scores on a scale			
arithmetic mean	78.0	79.0	29.0
standard deviation	± 5.53	± 6.76	± 1.17
Repeatable Battery for Assessment of Neurological Status (RBANS)			
RBANS is a tool to detect/characterize neurocognitive dementia changes in 5 neurocognitive domains; scores are 40-160 and higher scores indicate better cognitive functioning.			
Units: Scores on a scale			

arithmetic mean	104.4	108.7	102.6
standard deviation	± 12.03	± 12.83	± 12.22
Clinical Dementia Rating Sum of Boxes (CDR-SOB)			
Clinical Dementia Rating Sum of Boxes (CDR-SOB) measures cognition and functioning in 6 domains; scores are : 0-18 and higher scores indicate greater disease severity			
Units: scores on a scale			
arithmetic mean	0.10	0.04	0.16
standard deviation	± 0.276	± 0.209	± 0.404

Reporting group values	Cohort II (CII) CNP520 Placebo	Total	
Number of subjects	163	477	
Age Categorical			
Units: participants			
<=64 years	52	158	
65-69 years	65	206	
>70 years	46	113	
Sex: Female, Male			
Units: participants			
Female	102	275	
Male	61	202	
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	162	466	
Black	0	3	
Asian	0	4	
Pacific Islander	0	1	
Other	0	1	
Unknown	1	2	
API Preclinical Composite Cognitive Battery (APCC)			
APCC (API Preclinical Compo site Cognitive Battery) is a composite score derived from RBANS (Repeatable Battery for Assessment of Neurological Status), MMSE (Mini-Mental State Examination) and the Raven's Progressive Matrices; scores are 0-100 and higher scores indicate better cognitive performance.			
Units: Scores on a scale			
arithmetic mean	28.9		
standard deviation	± 1.33	-	
Repeatable Battery for Assessment of Neurological Status (RBANS)			
RBANS is a tool to detect/characterize neurocognitive dementia changes in 5 neurocognitive domains; scores are 40-160 and higher scores indicate better cognitive functioning.			
Units: Scores on a scale			
arithmetic mean	103.2		
standard deviation	± 12.03	-	
Clinical Dementia Rating Sum of Boxes (CDR-SOB)			
Clinical Dementia Rating Sum of Boxes (CDR-SOB) measures cognition and functioning in 6 domains; scores are : 0-18 and higher scores indicate greater disease severity			
Units: scores on a scale			
arithmetic mean	0.15		
standard deviation	± 0.417	-	

End points

End points reporting groups

Reporting group title	Cohort I (CI) CAD106
Reporting group description:	
CAD106 (450 µg) + Alum (450 µg) intra-muscular injection at Weeks 1, 7, 13 and every 13 weeks thereafter	
Reporting group title	Cohort I (CI) CAD106 Placebo
Reporting group description:	
Placebo to CAD106 + Alum (450 µg) intra-muscular injection at Weeks 1, 7, 13 and every 13 weeks thereafter	
Reporting group title	Cohort II (CII) CNP520
Reporting group description:	
CNP520 (50 mg) capsules taken once daily orally	
Reporting group title	Cohort II (CII) CNP520 Placebo
Reporting group description:	
Placebo to CNP520 capsules taken once daily orally	

Primary: Time to Event (diagnosis of mild cognitive impairment or dementia, due to Alzheimer's disease (AD))

End point title	Time to Event (diagnosis of mild cognitive impairment or dementia, due to Alzheimer's disease (AD))[1]
End point description:	
Event was defined as the first confirmed diagnosis of MCI due to Alzheimer's disease (AD) or dementia due to AD (whichever occurred first) after adjudication by the progression adjudication committee (PAC) as triggered either by an investigator diagnosis or an increase in the Clinical Dementia Rating (CDR) global score. An event had to be confirmed by the PAC at two consecutive visits. In case no confirmed event was observed for a participant, the observation was censored, and the censoring date was defined as the last date where the diagnostic classification was assessed. The Study was terminated and only confirmed events collected up to the data cut-off point were counted. Due to the early termination of the study only a small number of events were observed and time-to-event could not be analyzed. Kaplan-Meyer (KM) estimates were provided to estimate probability that a subject would have an event prior to the specified visit.	
End point type	Primary
End point timeframe:	
Baseline to end of exposure for a maximum of 1455 days for CI and 907 days for CII	
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: No analysis done	

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	249	163
Units: proportion of participants				
number (confidence interval 95%)				
Week 26 n=41,22,193, 126	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	0.98 (0.95 to 0.99)	0.98 (0.94 to 0.99)
Week 52 n=40,22,95,63	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	0.93 (0.88 to 0.96)	0.95 (0.90 to 0.98)
Week 78 n=37,21,18,9	0.97 (0.83 to 1.00)	1.00 (1.00 to 1.00)	0.88 (0.79 to 0.93)	0.85 (0.63 to 0.94)

Week 104 n=22,15,5,2	0.97 (0.83 to 1.00)	1.00 (1.00 to 1.00)	0.88 (0.79 to 0.93)	0.85 (0.63 to 0.94)

Statistical analyses

No statistical analyses for this end point

Primary: Change in the Alzheimer's Prevention Initiative Composite Cognitive (APCC) Test Score

End point title	Change in the Alzheimer's Prevention Initiative Composite Cognitive (APCC) Test Score[2]

End point description:

APCC is a composite score derived from the specific scores from the Repeatable Battery for the Assessment of Neurological Status (RBANS), Mini-Mental State Examination (MMSE) and the Raven's Progressive Matrices. The APCC score is a weighted score with ranges from from 0 to 100 where higher scores correspond to better cognitive performance.

End point type	Primary

End point timeframe:

CI = Baseline to Weeks 26, 52,78 104 and Baseline to last assessment; CII = Baseline to Weeks 26, 52, 78, 104 and Baseline to Last on-treatment and Baseline to Last off-treatment

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: No analysis done

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	249	163
Units: Total scores				
arithmetic mean (standard deviation)				
Week 26 n=41,23,154,105	-1.1 (± 4.10)	-2.0 (± 3.90)	-3.3 (± 4.54)	-1.0 (± 4.65)
Week 52 n=41,22,64,36	0.9 (± 4.24)	1.4 (± 3.36)	0.3 (± 4.27)	2.2 (± 6.11)
Week 78 n=27, 18,7,8	0.2 (± 4.15)	-0.7 (± 5.48)	-4.1 (± 4.14)	2.4 (± 4.23)
Week 104 n=17,9,3,0	-1.4 (± 4.67)	0.3 (± 4.00)	-6.7 (± 3.95)	9.999 (± 9.999)
CI-Last post BL assessment n=41,23,0,0	0.0 (± 4.62)	0.1 (± 3.87)	9.999 (± 9.999)	9.999 (± 9.999)
CII - Last on treatment n=0,0,179,125	9.999 (± 9.999)	9.999 (± 9.999)	-1.7 (± 4.81)	0.1 (± 4.58)
CII-Last off treatment n=0,0,166,90	9.999 (± 9.999)	9.999 (± 9.999)	-0.1 (± 4.72)	0.2 (± 4.56)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score

End point title	Change in Clinical Dementia Rating Scale Sum of Boxes (CDR-

	SOB) score

End point description:

The CDR was obtained through semi-structured interviews of participants and informants, and cognitive functioning was rated on a 5-point scale of functioning in six domains: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. The CDR global score ranged from zero to three, while the CDR-SOB was the sum of the ratings from the six domains, ranging from 0 to 18 with a minimum increment of 0.5. Higher scores indicated greater disease severity.

End point type	Secondary

End point timeframe:

CI = Baseline to Weeks 26, 52,78 104 and Baseline to last assessment; CII = Baseline to Weeks 26, 52, 78, 104 and Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	249	163
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 26 n=41,23,153,105	-0.04 (± 0.234)	0.00 (± 0.000)	0.04 (± 0.361)	0.00 (± 0.336)
Week 52 n=41,23,64,36	-0.01 (± 0.237)	0.02 (± 0.104)	-0.02 (± 0.281)	-0.08 (± 0.541)
Week 78 n=27,18,7,7	-0.04 (± 0.237)	0.03 (± 0.118)	0.14 (± 0.802)	-0.14 (± 0.244)
Week 104 n=17,9,3,0	0.15 (± 0.460)	0.06 (± 0.167)	-0.17 (± 0.764)	9.999 (± 9.999)
CI Last post baseline assessment n=41,23,0,0	0.04 (± 0.343)	0.00 (± 0.302)	9.999 (± 9.999)	9.999 (± 9.999)
CII Last on-treatment n=0,0,174,122	9.999 (± 9.999)	9.999 (± 9.999)	0.06 (± 0.505)	0.03 (± 0.410)
CII Last off-treatment n=0,0,156,90	9.999 (± 9.999)	9.999 (± 9.999)	0.05 (± 0.464)	-0.01 (± 0.519)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Total scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

End point title	Change in the Total scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

End point description:

Repeatable Battery for the Assessment of Neurological Status (RBANS) is a clinical tool designed to detect and characterize the earliest neurocognitive changes associated with dementia. The RBANS generates age-adjusted index scores for five neurocognitive domains: Immediate Memory, Visuospatial/Constructional, Language, Attention and Delayed Memory, which are used to calculate a Total Scale Index score. Index scores and total score range from 40 to 160 and a higher score indicates better cognitive functioning.

End point type	Secondary

End point timeframe:

CI = Baseline to Weeks 26, 52,78 104 and Baseline to last assessment; CII = Baseline to Weeks 26, 52, 78, 104 and Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	249	163
Units: scores				
arithmetic mean (standard deviation)				
Total Week 26 n=41,23,154,105	-5.1 (± 7.25)	-3.0 (± 7.51)	-4.1 (± 8.58)	-2.6 (± 7.83)
Total Week 52 n=41,22,64,37	-1.2 (± 7.82)	4.5 (± 7.10)	-0.1 (± 7.91)	1.4 (± 8.06)
Total Week 78 n=27,18,7,8	-2.1 (± 7.69)	-4.0 (± 7.82)	-12.1 (± 7.40)	-4.8 (± 5.99)
Total Week 104 n=17,9,3,0	-1.4 (± 6.74)	-3.0 (± 8.34)	-7.7 (± 15.57)	9.999 (± 9.999)
Total CI Last post baseline assessment n=41,23,0,0	-1.0 (± 9.27)	0.4 (± 7.20)	9.999 (± 9.999)	9.999 (± 9.999)
Total CII Last on-treatment n=0,0,209,141	9.999 (± 9.999)	9.999 (± 9.999)	-2.7 (± 8.65)	-0.2 (± 9.22)
Total CII Last off-treatment n=0,0,169,93	9.999 (± 9.999)	9.999 (± 9.999)	-1.5 (± 9.20)	-0.6 (± 8.83)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Index scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

End point title	Change in the Index scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

End point description:

Repeatable Battery for the Assessment of Neurological Status (RBANS) is a clinical tool designed to detect and characterize the earliest neurocognitive changes associated with dementia. The RBANS generates age-adjusted index scores for five neurocognitive domains: Immediate Memory, Visuospatial/Constructional, Language, Attention and Delayed Memory, which are used to calculate a Total Scale Index score. Index scores and total score range from 40 to 160 and a higher score indicates better cognitive functioning.

End point type	Secondary

End point timeframe:

CI = Baseline to Weeks 26, 52 and Baseline to last assessment; CII = Baseline to Weeks 26, 52 and Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	249	163
Units: scores				
arithmetic mean (standard deviation)				
Immediate memory - Week 26 n=41,23,154,105	-8.6 (± 10.68)	-3.8 (± 11.16)	-7.4 (± 13.11)	-3.7 (± 12.15)

Immediate memory - Week 52 n=41,22,64,37	1.3 (± 10.81)	4.8 (± 8.68)	0.6 (± 13.55)	5.1 (± 11.73)
CI Immediate memory-Last post BL asses n=41,23,0,0	-1.1 (± 13.11)	1.1 (± 14.52)	9.999 (± 9.999)	9.999 (± 9.999)
CII Immediate memory-Last on-treat n=0,0,209,141	9.999 (± 9.999)	9.999 (± 9.999)	-3.7 (± 14.43)	0.6 (± 13.54)
CII Immediate memory-Last off-treat n=0,0,169,93	9.999 (± 9.999)	9.999 (± 9.999)	-3.2 (± 13.76)	-2.0 (± 11.90)
Visuospatial Week 26 n=41,23,154,105	-6.5 (± 15.21)	0.7 (± 12.39)	-3.5 (± 14.98)	-2.4 (± 13.00)
Visuospatial Week 52 n=41,22,64,37	-6.5 (± 14.59)	3.0 (± 15.09)	-1.4 (± 14.29)	-4.8 (± 12.60)
CI Visuospatial Last post BL assess n=41,23,0,0	-4.7 (± 13.91)	1.9 (± 12.72)	9.999 (± 9.999)	9.999 (± 9.999)
CII Visuospatial Last on-treat n=0,0,209,141	9.999 (± 9.999)	9.999 (± 9.999)	-3.5 (± 14.59)	-2.6 (± 14.92)
CII Visuospatial Last off-treatment n=0,0,169,93	9.999 (± 9.999)	9.999 (± 9.999)	-1.2 (± 15.13)	-0.8 (± 15.18)
Language Week 26 n=41,23,154,105	-1.4 (± 12.91)	-2.8 (± 11.42)	-0.1 (± 12.05)	-1.5 (± 11.87)
Language Week 52 n=41,22,64,37	2.6 (± 10.29)	2.0 (± 11.51)	-0.3 (± 12.88)	0.8 (± 9.72)
CI Language Last post BL assess n=41,23,0,0	1.9 (± 13.00)	-4.5 (± 12.86)	9.999 (± 9.999)	9.999 (± 9.999)
CII Language Last on-treat n=0,0,209,141	9.999 (± 9.999)	9.999 (± 9.999)	-0.1 (± 12.07)	-0.1 (± 11.93)
CII Language Last off-treatment n=0,0,169,93	9.999 (± 9.999)	9.999 (± 9.999)	-1.0 (± 13.19)	-1.8 (± 11.25)
Attention Week 26 n=41,23,154,105	1.8 (± 9.40)	-0.6 (± 14.19)	-0.7 (± 10.42)	-0.6 (± 11.67)
Attention Week 52 n=41,22,64,37	0.9 (± 10.80)	-0.5 (± 13.09)	-0.2 (± 10.02)	2.7 (± 10.77)
CI Attention Last post BL assess n=41,23,0,0	2.0 (± 12.91)	2.0 (± 10.25)	9.999 (± 9.999)	9.999 (± 9.999)
CII Attention Last on-treat n=0,0,209,141	9.999 (± 9.999)	9.999 (± 9.999)	0.1 (± 10.80)	0.8 (± 11.20)
CII-Attention Last off-treat n=0,0,169,93	9.999 (± 9.999)	9.999 (± 9.999)	1.0 (± 1.64)	1.2 (± 11.07)
Delayed memory - Week 26 n=41,23,154,105	-3.8 (± 7.83)	-2.7 (± 7.64)	-3.8 (± 11.20)	-2.6 (± 8.85)
Delayed memory - Week 52 n=41,22,64,37	-2.0 (± 8.01)	3.2 (± 6.23)	2.3 (± 9.09)	0.6 (± 11.73)
CI Delayed memory-Last post BL assess n=41,23,0,0	-1.0 (± 10.20)	1.3 (± 8.44)	9.999 (± 9.999)	9.999 (± 9.999)
CII Delayed memory-Last on-treat n=0,0,209,141	9.999 (± 9.999)	9.999 (± 9.999)	-2.5 (± 10.61)	0.4 (± 10.28)
CII Delayed memory Last off-treat n=0,0,169,93	9.999 (± 9.999)	9.999 (± 9.999)	-1.1 (± 10.75)	1.1 (± 11.28)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Everyday Cognition scale (ECog-Subject) total scores

End point title	Change in the Everyday Cognition scale (ECog-Subject) total scores

End point description:

Everyday Cognition Scale (ECog) measures cognitively-relevant everyday abilities comprised of 39 items covering 6 cognitively-relevant domains: Everyday Memory, Everyday Language, Everyday Visuospatial Abilities, Everyday Planning, Everyday Organization, and Everyday Divided Attention. The questionnaire is a self-reported measure completed by both participant and study partner (informant). The total score for the 39 items ranges from 39 to 195, with greater scores indicating worse daily function.

End point type	Secondary

End point timeframe:

CI = Baseline to Weeks 26, 52 and Baseline to last assessment; CII = Baseline to Weeks 26, 52 and Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	249	163
Units: Total scores				
arithmetic mean (standard deviation)				
Week 26	-1.0 (± 2.94)	2.3 (± 4.80)	1.8 (± 6.03)	0.6 (± 6.45)
Week 52	0.6 (± 5.23)	0.4 (± 2.99)	2.7 (± 6.16)	0.2 (± 5.01)
CI Last post baseline assessment	0.6 (± 5.02)	1.6 (± 4.07)	9.999 (± 9.999)	9.999 (± 9.999)
CII Last on-treatment	9.999 (± 9.999)	9.999 (± 9.999)	2.6 (± 7.81)	0.9 (± 6.48)
CII Last off-treatment	9.999 (± 9.999)	9.999 (± 9.999)	1.6 (± 6.77)	0.8 (± 6.13)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Everyday Cognition scale (ECog-Informant) total scores

End point title	Change in the Everyday Cognition scale (ECog-Informant) total scores

End point description:

Everyday Cognition Scale (ECog) measures cognitively-relevant everyday abilities comprised of 39 items covering 6 cognitively-relevant domains: Everyday Memory, Everyday Language, Everyday Visuospatial Abilities, Everyday Planning, Everyday Organization, and Everyday Divided Attention. The questionnaire is a self-reported measure completed by both participant and study partner (informant). The total score for the 39 items ranges from 39 to 195, with greater scores indicating worse daily function. Cohort I=C I and Cohort II=C II.

End point type	Secondary

End point timeframe:

CI = Baseline to Weeks 26, 52 and Baseline to last assessment; CII = Baseline to Weeks 26, 52 and Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	249	163
Units: Total scores				
arithmetic mean (standard deviation)				
Week 26 n=37,23,142,95	-0.4 (± 4.21)	-1.0 (± 4.87)	0.1 (± 6.84)	-0.7 (± 8.69)
Week 52 n=37,22,57,29	-0.2 (± 3.15)	-0.3 (± 5.12)	1.4 (± 5.18)	-0.2 (± 9.59)

CI Last post baseline assessment	-1.1 (± 4.23)	-1.0 (± 4.88)	9.999 (± 9.999)	9.999 (± 9.999)
CII Last on-treatment n=0,0,160,113	9.999 (± 9.999)	9.999 (± 9.999)	1.3 (± 8.76)	0.1 (± 9.12)
CII Last off-treatment n=0,0,143,77	9.999 (± 9.999)	9.999 (± 9.999)	1.4 (± 8.49)	-0.5 (± 10.10)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with newly occurring safety MRI abnormalities (ARIA-E, ARIA-H,white matter disease and any other MRI abnormalities)

End point title	Number of participants with newly occurring safety MRI abnormalities (ARIA-E, ARIA-H,white matter disease and any other MRI abnormalities)

End point description:

Safety MRI included sequences necessary for ascertainment of possible ARIA-E (Amyloid Related Imaging AbnormalityEdema), ARIA-H (Amyloid Related Imaging Abnormality- Hemorrhage, including superficial siderosis and microhemorrhages), assessment of recent infarcts and white matter integrity examination (White matter disease worsening since baseline) and a general assessment of brain abnormalities. Assessment of cerebral amyloid angiopathy (CAA) is included in the overall safety MRI findings results. Presence of ARIA-H is >4 microhemorrhages (new hemosiderin deposits < 10 mm)

End point type	Secondary

End point timeframe:

Baseline to end of exposure for a maximum of 1455 days for CI and 907 days for CII

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	249	163
Units: participants				
Questionable presence of ARIA-E	0	0	0	1
Presence of ARIA-E	1	0	0	2
ARIA-E - If present, the worst Severity=moderate	1	0	0	2
Presence of ARIA-H	2	0	6	2
White matter disease worsening: 1-3 increase	0	2	6	1
White matter disease worsening: 4 - 8 increase	0	0	0	0
White matter disease worsening >8 increase	0	0	0	0
Any other MRI abnormalities	2	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized percent change on volume of brain regions

End point title	Annualized percent change on volume of brain regions

End point description:

Annualized % change from baseline in volume of specific brain regions of interest (ROIs): whole brain (WB), hippocampus (Hip), and lateral ventricles (LV). Annualized percentage change was calculated as (percentage per participant / time interval (in days)) x 365.25. Time interval (in days) was derived as date of current MRI assessment on study drug - date of baseline MRI assessment + 1.

End point type	Secondary

End point timeframe:

CI = Baseline to Weeks 26, 52 and Baseline to last assessment; CII = Baseline to Weeks 26, 52 and Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	201	135
Units: Percentage of volume change				
arithmetic mean (standard deviation)				
WB Week 26 n=35,23,145,104	-0.7570 (± 1.33114)	-0.6044 (± 1.29608)	-0.9318 (± 1.06843)	-0.4616 (± 1.00537)
WB Week 52 n=37,22,63,40	-0.5144 (± 0.66578)	-0.3395 (± 0.75810)	-0.6590 (± 0.64838)	-0.4227 (± 0.58778)
WB CI Last post baseline assessment n=40,23,0,0	-0.4645 (± 0.57503)	-0.5321 (± 0.46526)	9.999 (± 9.999)	9.999 (± 9.999)
WB CII Last on-treatment n=0,0,148,108	9.999 (± 9.999)	9.999 (± 9.999)	-0.8268 (± 0.94889)	-0.5181 (± 0.92086)
WB CII Last off-treatment n=0,0,36,23	9.999 (± 9.999)	9.999 (± 9.999)	-0.6748 (± 0.62542)	-0.3317 (± 0.62616)
Hip Week 26 n=35,23,145,104	-1.3262 (± 2.35453)	-0.9245 (± 2.81731)	-1.6603 (± 2.65529)	-0.8817 (± 2.06227)
Hip Week 52 n=37,22,63,40	-1.0376 (± 1.44310)	-0.7780 (± 1.81604)	-1.2438 (± 1.79988)	-0.9567 (± 1.42941)
Hip CI Last post baseline assessment n=40,23,0,0	-1.0801 (± 1.38061)	-1.0477 (± 1.33603)	9.999 (± 9.999)	9.999 (± 9.999)
Hip CII Last on-treatment n=0,0,148,108	9.999 (± 9.999)	9.999 (± 9.999)	-1.4790 (± 2.36526)	-0.9984 (± 1.85655)
Hip CII Last off-treatment n=0,0,36,23	9.999 (± 9.999)	9.999 (± 9.999)	-1.9375 (± 2.03593)	-1.0498 (± 1.66596)
LV Week 26 n=35,23,145,104	4.1848 (± 5.77286)	2.5581 (± 7.54667)	4.5176 (± 5.59748)	3.9735 (± 4.23237)
LV Week 52 n=37,22,63,40	4.2060 (± 3.92877)	2.8232 (± 5.04358)	3.3854 (± 3.71214)	2.9059 (± 3.18734)
LV CI Last post baseline assessment n=40,23,0,0	4.0543 (± 3.75310)	3.5427 (± 3.53772)	9.999 (± 9.999)	9.999 (± 9.999)
LV CII Last on-treatment n=0,0,148,108	9.999 (± 9.999)	9.999 (± 9.999)	4.3588 (± 5.07839)	4.0308 (± 3.64102)
LV CII Last off-treatment n=0,0,36,23	9.999 (± 9.999)	9.999 (± 9.999)	3.9617 (± 2.61831)	2.6052 (± 3.54903)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in cerebrospinal fluid (CSF) levels of Amyloid Beta 40 (Aβ40)

End point title	Change in cerebrospinal fluid (CSF) levels of Amyloid Beta 40 (Aβ40)

End point description:

Alzheimer's Disease-related biomarkers analyzed in cerebrospinal fluid (CSF): Amyloid Beta 40 (Aβ40)

End point type	Secondary

End point timeframe:

Baseline to last assessment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[3]	0[4]	0[5]	0[6]
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[3] - No post baseline data available

[4] - No post baseline data available

[5] - No post baseline data available

[6] - No post baseline data available

Statistical analyses

No statistical analyses for this end point

Secondary: Change in cerebrospinal fluid (CSF) levels of Amyloid Beta 42 (Aβ42)

End point title	Change in cerebrospinal fluid (CSF) levels of Amyloid Beta 42 (Aβ42)

End point description:

Alzheimer's Disease-related biomarkers analyzed in cerebrospinal fluid (CSF): Amyloid Beta 42 (Aβ42)

End point type	Secondary

End point timeframe:

Baseline to last assessment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[7]	0[8]	0[9]	0[10]
Units: pg/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[7] - No post baseline data available

[8] - No post baseline data available

[9] - No post baseline data available

[10] - No post baseline data available

Statistical analyses

No statistical analyses for this end point

Secondary: Change in cerebrospinal fluid (CSF) levels of total tau and phosphorylated tau

End point title	Change in cerebrospinal fluid (CSF) levels of total tau and phosphorylated tau

End point description:

Alzheimer's Disease-related biomarkers analyzed in cerebrospinal fluid (CSF): total tau protein and phosphorylated tau protein levels

End point type	Secondary

End point timeframe:

Baseline to last assessment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[11]	0[12]	0[13]	0[14]
Units: pg/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[11] - No post baseline data available

[12] - No post baseline data available

[13] - No post baseline data available

[14] - No post baseline data available

Statistical analyses

No statistical analyses for this end point

Secondary: Change in neurofibrillary tangle burden as measured by standardized uptake ratio (SUVR) of PET scans with tau radiotracer (where available)

End point title	Change in neurofibrillary tangle burden as measured by standardized uptake ratio (SUVR) of PET scans with tau radiotracer (where available)

End point description:

To demonstrate the effects of CAD106 and CNP520 vs placebo on tau pathology in the brain

End point type	Secondary

End point timeframe:

Baseline to last assessment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[15]	0[16]	0[17]	0[18]
Units: SUVR				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[15] - No post baseline data available

[16] - No post baseline data available

[17] - No post baseline data available

[18] - No post baseline data available

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I : Annualized change in amyloid deposition as measured by centiloids of positron emission tomography (PET) scan with amyloid radiotracer

End point title	Cohort I : Annualized change in amyloid deposition as measured by centiloids of positron emission tomography (PET) scan with amyloid radiotracer[19]

End point description:

To demonstrate the effects of CAD106 vs placebo on Alzheimer’s Disease-related biomarkers

End point type	Secondary

End point timeframe:

Baseline up to approximately Week 104

Notes:

[19] - 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: Only available for CAD106

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	23		
Units: Centiloids				
arithmetic mean (standard deviation)	-0.911 (± 5.6596)	8.367 (± 6.6805)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Serum Neurofilaments

End point title	Change in Serum Neurofilaments

End point description:

Alzheimer's Disease-related biomarkers analyzed in blood serum: light chain neurofilaments (NfL)

End point type	Secondary

End point timeframe:

Baseline to Week 26 and week 52, CI baseline to last assessment. CII baseline to last on-treatment and to last off-treatment

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	249	163
Units: pg/mL				
arithmetic mean (standard deviation)				
Week 26	1.44 (± 3.165)	-3.89 (± 13.058)	0.644 (± 3.4879)	0.362 (± 6.7547)
Week 52	2.63 (± 5.716)	-6.09 (± 16.542)	1.921 (± 4.0515)	-4.852 (± 14.2270)
C I Last post baseline assessment	1.77 (± 4.643)	-3.31 (± 12.858)	9.999 (± 9.999)	9.999 (± 9.999)
C II Last on-treatment	9.999 (± 9.999)	9.999 (± 9.999)	0.647 (± 3.5357)	0.280 (± 6.8289)
C II Last off-treatment	9.999 (± 9.999)	9.999 (± 9.999)	-0.004 (± 3.7102)	-2.145 (± 2.6799)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of suicidal ideation or behavior events

End point title	Number of suicidal ideation or behavior events

End point description:

Prospective suicidality assessment was performed with the use of Columbia-Suicide Severity Rating Scale (C-SSRS), a questionnaire using a detailed branched logic algorithm evaluating participant's suicidality ideation and behavior. Answer "yes" on item 4 or 5 of the Suicidal Ideation section or "yes" on any item of the Suicidal Behavior section was considered positive.

End point type	Secondary

End point timeframe:

Baseline to end of exposure for a maximum of 1455 days for CI and 907 days for CII

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	23	249	163
Units: events				
Any suicidal ideation	2	1	12	4

Any suicidal behavior	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I : change in cognition as measured by APCC and CDR-SOB scores and antibody response

End point title	Cohort I : change in cognition as measured by APCC and CDR-SOB scores and antibody response

End point description:

End point type	Secondary

End point timeframe:

Month 6 to Month 60

End point values	Cohort I (CI) CAD106	Cohort I (CI) CAD106 Placebo	Cohort II (CII) CNP520	Cohort II (CII) CNP520 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[20]	0[21]	0[22]	0[23]
Units: scores				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[20] - No post baseline data available

[21] - No post baseline data available

[22] - No post baseline data available

[23] - No post baseline data available

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I: Peak concentration (Cmax) of CAD106 induced Abeta-specific antibody titers

End point title	Cohort I: Peak concentration (Cmax) of CAD106 induced Abeta-specific antibody titers[24]

End point description:

Cmax is the maximum Titer Concentration of any post-baseline 'on treatment' visit. A visit is considered as
'on treatment' if visit date is within {last injection + 180 days}.
- Geometric mean and CI’s are back-transformed from the estimates for Log mean and CI’s.

End point type	Secondary

End point timeframe:

Week 9, 13, 15, 26 and quarterly thereafter (trough values)

Notes:

[24] - 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: Outcome objectiive only for CAD106

End point values	Cohort I (CI) CAD106			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: units/mL				
geometric mean (confidence interval 95%)	128.76 (99.05 to 167.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I: Area under the concentration curve (AUC) of CAD106 induced Abeta-specific antibody titers

End point title	Cohort I: Area under the concentration curve (AUC) of CAD106 induced Abeta-specific antibody titers[25]

End point description:

AUC is calculated based on 'on treatment' visit only.(missing values for peak visits were linearly interpolated for
calculation; missing values for trough visits were imputed by average of non-missing trough values.).

End point type	Secondary

End point timeframe:

Week 9, 13, 15, 26 and quarterly thereafter (trough values)

Notes:

[25] - 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: Outcome objective only for CAD106

End point values	Cohort I (CI) CAD106			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: integral				
number (confidence interval 95%)	34999.89 (22992.17 to 53278.68)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were reported from first dose of study treatment plus 31 days of washout period for a maximum duration of 1455 days for CI and 907 days for CII	
Adverse event reporting additional description:	
Frequency threshold was 2.5 (system will not accept decimal)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Cohort I @CAD106
Reporting group description:	
Cohort I @CAD106	
Reporting group title	Cohort I @Placebo
Reporting group description:	
Cohort I @Placebo	
Reporting group title	Cohort II @CNP520 50 mg
Reporting group description:	
Cohort II @CNP520 50 mg	
Reporting group title	Cohort II @Placebo
Reporting group description:	
Cohort II @Placebo	

Serious adverse events	Cohort I @CAD106	Cohort I @Placebo	Cohort II @CNP520 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 42 (9.52%)	3 / 23 (13.04%)	8 / 249 (3.21%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	1 / 42 (2.38%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 42 (2.38%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fall			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	0 / 249 (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
Femoral neck fracture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	0 / 249 (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
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	0 / 249 (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
Coronary artery disease			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Cerebellar haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	0 / 249 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	0 / 249 (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
Syncope			
subjects affected / exposed	1 / 42 (2.38%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Feeling jittery			
subjects affected / exposed	1 / 42 (2.38%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Hiatus hernia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 42 (2.38%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	0 / 249 (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
Pulmonary mass			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	0 / 249 (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
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	0 / 249 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			

subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	0 / 249 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort II @Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 163 (4.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial flutter				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stress cardiomyopathy				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebellar haemorrhage				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Feeling jittery				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Hiatus hernia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Nausea			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Cohort I @CAD106	Cohort I @Placebo	Cohort II @CNP520 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 42 (85.71%)	21 / 23 (91.30%)	106 / 249 (42.57%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	3	0	0
Benign neoplasm of thyroid gland			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Haemangioma of liver			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Melanocytic naevus			
subjects affected / exposed	1 / 42 (2.38%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	1	1	0
Uterine leiomyoma			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			

Chills			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	11 / 42 (26.19%)	1 / 23 (4.35%)	3 / 249 (1.20%)
occurrences (all)	13	1	3
Influenza like illness			
subjects affected / exposed	5 / 42 (11.90%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	5	0	0
Injection site erythema			
subjects affected / exposed	1 / 42 (2.38%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	1	1	0
Injection site pain			
subjects affected / exposed	10 / 42 (23.81%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	12	0	0
Injection site pruritus			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	2	0	0
Injection site reaction			
subjects affected / exposed	4 / 42 (9.52%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	5	0	0
Malaise			
subjects affected / exposed	3 / 42 (7.14%)	1 / 23 (4.35%)	1 / 249 (0.40%)
occurrences (all)	3	1	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	7 / 42 (16.67%)	1 / 23 (4.35%)	4 / 249 (1.61%)
occurrences (all)	15	2	4
Immune system disorders			
Seasonal allergy			

subjects affected / exposed	2 / 42 (4.76%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	2	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 42 (7.14%)	0 / 23 (0.00%)	5 / 249 (2.01%)
occurrences (all)	3	0	5
Oropharyngeal pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	4 / 249 (1.61%)
occurrences (all)	0	1	4
Throat irritation			
subjects affected / exposed	1 / 42 (2.38%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	2 / 42 (4.76%)	1 / 23 (4.35%)	19 / 249 (7.63%)
occurrences (all)	2	1	19
Anxiety			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	11 / 249 (4.42%)
occurrences (all)	0	0	13
Insomnia			
subjects affected / exposed	2 / 42 (4.76%)	1 / 23 (4.35%)	4 / 249 (1.61%)
occurrences (all)	2	1	4
Irritability			
subjects affected / exposed	1 / 42 (2.38%)	1 / 23 (4.35%)	2 / 249 (0.80%)
occurrences (all)	1	1	2
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Lumbar puncture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Urine albumin/creatinine ratio increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	9 / 249 (3.61%)
occurrences (all)	0	0	9
Weight decreased			

subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	7 / 249 (2.81%)
occurrences (all)	0	0	7
Weight increased			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	2 / 249 (0.80%)
occurrences (all)	0	1	2
Contusion			
subjects affected / exposed	3 / 42 (7.14%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences (all)	4	0	1
Fall			
subjects affected / exposed	4 / 42 (9.52%)	1 / 23 (4.35%)	8 / 249 (3.21%)
occurrences (all)	7	1	10
Injection related reaction			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	3	0	0
Mallet finger			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Meniscus injury			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Pelvic fracture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Type V hyperlipidaemia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 42 (0.00%)	2 / 23 (8.70%)	1 / 249 (0.40%)
occurrences (all)	0	2	1
Atrial flutter			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	2	0
Palpitations			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Carpal tunnel syndrome			
subjects affected / exposed	1 / 42 (2.38%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	1	1	0
Cerebral cyst			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Cervical radiculopathy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	1 / 249 (0.40%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	7 / 249 (2.81%)
occurrences (all)	0	0	7
Headache			
subjects affected / exposed	7 / 42 (16.67%)	0 / 23 (0.00%)	6 / 249 (2.41%)
occurrences (all)	9	0	7
Lethargy			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	2 / 249 (0.80%)
occurrences (all)	2	0	3
Paraesthesia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 23 (4.35%)	2 / 249 (0.80%)
occurrences (all)	1	2	3
Presyncope			

subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	1 / 249 (0.40%)
occurrences (all)	0	1	1
Radiculopathy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	2	0	0
Tinnitus			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	3 / 249 (1.20%)
occurrences (all)	3	0	3
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Vitreous detachment			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 42 (0.00%)	2 / 23 (8.70%)	0 / 249 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	3 / 42 (7.14%)	0 / 23 (0.00%)	7 / 249 (2.81%)
occurrences (all)	5	0	9
Diarrhoea			
subjects affected / exposed	3 / 42 (7.14%)	1 / 23 (4.35%)	6 / 249 (2.41%)
occurrences (all)	3	1	7
Eosinophilic oesophagitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	5 / 249 (2.01%)
occurrences (all)	2	0	5
Pancreatic cyst			

subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Salivary gland disorder			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences (all)	2	0	2
Nail disorder			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 42 (0.00%)	0 / 23 (0.00%)	10 / 249 (4.02%)
occurrences (all)	0	0	14
Urticaria			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	1 / 42 (2.38%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	1	1	0
Hypercalciuria			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	2	0	0
Thyroid mass			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	4 / 42 (9.52%)	1 / 23 (4.35%)	6 / 249 (2.41%)
occurrences (all)	4	1	7
Back pain			
subjects affected / exposed	4 / 42 (9.52%)	0 / 23 (0.00%)	7 / 249 (2.81%)
occurrences (all)	5	0	7
Exostosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Flank pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Foot deformity			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	5 / 249 (2.01%)
occurrences (all)	2	0	6
Musculoskeletal pain			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences (all)	2	0	1
Musculoskeletal stiffness			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	1 / 249 (0.40%)
occurrences (all)	2	0	1
Myalgia			
subjects affected / exposed	3 / 42 (7.14%)	3 / 23 (13.04%)	3 / 249 (1.20%)
occurrences (all)	3	3	3
Osteoarthritis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	2	0
Pain in extremity			
subjects affected / exposed	4 / 42 (9.52%)	2 / 23 (8.70%)	6 / 249 (2.41%)
occurrences (all)	5	2	6
Rotator cuff syndrome			
subjects affected / exposed	2 / 42 (4.76%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	2	1	0

Tendonitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	1 / 249 (0.40%)
occurrences (all)	0	1	1
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 42 (0.00%)	2 / 23 (8.70%)	1 / 249 (0.40%)
occurrences (all)	0	2	1
Bronchitis			
subjects affected / exposed	2 / 42 (4.76%)	1 / 23 (4.35%)	1 / 249 (0.40%)
occurrences (all)	2	1	1
Cellulitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis bacterial			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Dacryocanaliculitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	0 / 249 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 42 (0.00%)	1 / 23 (4.35%)	1 / 249 (0.40%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	1 / 42 (2.38%)	2 / 23 (8.70%)	3 / 249 (1.20%)
occurrences (all)	1	2	3
Nasopharyngitis			
subjects affected / exposed	4 / 42 (9.52%)	2 / 23 (8.70%)	10 / 249 (4.02%)
occurrences (all)	4	2	12
Pharyngitis			
subjects affected / exposed	1 / 42 (2.38%)	1 / 23 (4.35%)	1 / 249 (0.40%)
occurrences (all)	1	1	1
Respiratory tract infection			

subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	2	0	0
Sinusitis			
subjects affected / exposed	3 / 42 (7.14%)	1 / 23 (4.35%)	5 / 249 (2.01%)
occurrences (all)	3	1	6
Upper respiratory tract infection			
subjects affected / exposed	7 / 42 (16.67%)	3 / 23 (13.04%)	11 / 249 (4.42%)
occurrences (all)	8	4	11
Urinary tract infection			
subjects affected / exposed	0 / 42 (0.00%)	2 / 23 (8.70%)	5 / 249 (2.01%)
occurrences (all)	0	2	5
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	2 / 42 (4.76%)	0 / 23 (0.00%)	0 / 249 (0.00%)
occurrences (all)	2	0	0
Vitamin B12 deficiency			
subjects affected / exposed	1 / 42 (2.38%)	2 / 23 (8.70%)	4 / 249 (1.61%)
occurrences (all)	1	2	4

Non-serious adverse events	Cohort II @Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 163 (46.63%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	2		
Benign neoplasm of thyroid gland			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Haemangioma of liver			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Melanocytic naevus			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Uterine leiomyoma			

subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Injection site erythema			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Injection site pruritus			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Injection site reaction			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Oedema peripheral			

subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Throat irritation			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	5 / 163 (3.07%)		
occurrences (all)	6		
Anxiety			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	9 / 163 (5.52%)		
occurrences (all)	10		
Irritability			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		

Lumbar puncture			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Urine albumin/creatinine ratio increased			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences (all)	4		
Contusion			
subjects affected / exposed	3 / 163 (1.84%)		
occurrences (all)	4		
Fall			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences (all)	4		
Injection related reaction			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Mallet finger			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Meniscus injury			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Pelvic fracture			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Skin abrasion			

subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Type V hyperlipidaemia			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Atrial flutter			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Carpal tunnel syndrome			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Cerebral cyst			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Cervical radiculopathy			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	9 / 163 (5.52%)		
occurrences (all)	9		
Lethargy			

subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Radiculopathy			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Tinnitus			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Vitreous detachment			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	3 / 163 (1.84%)		
occurrences (all)	3		
Eosinophilic oesophagitis			

subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	4 / 163 (2.45%) 4		
Pancreatic cyst subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0		
Salivary gland disorder subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Dermatitis contact subjects affected / exposed occurrences (all)	2 / 163 (1.23%) 3		
Nail disorder subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	5 / 163 (3.07%) 6		
Urticaria subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0		
Renal and urinary disorders			
Cystitis haemorrhagic subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0		
Dysuria subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0		
Hypercalciuria subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0		
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Thyroid mass			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 163 (4.29%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	6		
Exostosis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Foot deformity			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	3 / 163 (1.84%)		
occurrences (all)	4		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Osteoarthritis			

subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	5 / 163 (3.07%)		
occurrences (all)	6		
Rotator cuff syndrome			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Tendonitis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	8 / 163 (4.91%)		
occurrences (all)	9		
Cellulitis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Conjunctivitis bacterial			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Dacryocanaliculitis			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		

Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	2 / 163 (1.23%) 2 0 / 163 (0.00%) 0 1 / 163 (0.61%) 1 8 / 163 (4.91%) 12 11 / 163 (6.75%) 13 4 / 163 (2.45%) 5		
Metabolism and nutrition disorders Hyperlipidaemia subjects affected / exposed occurrences (all) Vitamin B12 deficiency subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0 0 / 163 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2015	This amendment addressed the Special Protocol Assessment comments received from the US Food and Drug Administration (FDA) on 18-Sep-2015.
30 September 2016	This amendment addressed the activation of Cohort II (CNP520 and matching placebo). The amendment also included some clarifications of the protocol following feedback from Investigators, health authorities and ethics committees on the previous version.
30 June 2017	This amendment included: The consolidation of the changes required by the UK Health Authority (MHRA) dated 24 January 2017 and the German Health Authorities (BfArM and PEI) dated 17 February 2017; Allowance for PET tracer other than 18F-florbetapir (e.g. 18F-flutemetamol and 18F-florbetaben) or substitution with Aβ measurement from cerebrospinal fluid (CSF) sampling if amyloid PET scan/tracer is unavailable; Prioritization of cohort recruitment for Cohort II defined by 1:4 ratio for Cohort I:Cohort II until Cohort II was fully recruited in order to enable a concurrent read-out of Cohort II and the parallel study with CNP520 (CCNP520A2202J – Generation Study 2); A randomization halt to Cohort I was introduced to mitigate the risk that a large number of participants are exposed to CAD106 prior to the futility analysis on CNS activity. Additionally, feedback from Investigators, other health authorities and ethics committees in other countries and updates for consistency with Study CCNP520A2202J were incorporated.
30 November 2017	This amendment included: Alignment with recent CNP520 IB update (Edition 4 released 25-Aug-2017) reflecting new data from which eliminated need for male contraception, no relevant QT prolongation by CNP520 therefore current cardiac monitoring was adequate, inclusion of tau PET assessments to neurofibrillary tangle burden, randomization halt to Cohort to mitigate risk to patients prior to futility analysis regarding CNS activitiy.
18 December 2018	This amendment followed a Letter to Investigators issued on November 13, 2018 and included the changes implemented according to USM plan as required for participant safety monitoring. (per ICH GCP 3.3.7; 4.5.4. and European Commission guidance (2010/C 82/01) 3.9); dose regimen modification.
30 January 2020	This amendment documents, for completeness, the changes regarding follow-up of participants after early termination of the study according to the Investigators Notifications distributed between July-2019 and December-2019. The changes related to discontinuation of treatment with CNP520 were already formally communicated via an Urgent Safety Measure (USM) dated 11-Jul-2019.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, of which EMA is aware, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: