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

Summary

EudraCT number	2016-002976-28
Trial protocol	ES DE BE FI IS PT NL GB FR IT
Global end of trial date	26 March 2020

Results information

Result version number	v1 (current)
This version publication date	12 April 2021
First version publication date	12 April 2021

Trial information

Trial identification

Sponsor protocol code	CCNP520A2202J

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03131453
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Novartis Pharma AG, Clinical Disclosure Office, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Novartis Pharma AG, Clinical Disclosure Office, 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	26 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the trial were to demonstrate the effect of CNP520 vs. placebo on time to diagnosis of mild cognitive impairment (MCI) due to AD or dementia due to AD, whichever occurs first during the course of the study and to demonstrate the effect of CNP520 vs. placebo on cognition using API Preclinical Composite Cognitive Battery (APCC). The study was terminated early due to unexpected, mild, early worsening in measures of cognitive function, increased brain volume loss, and greater mean body weight loss on CNP520 compared to placebo. Treatment was stopped due to an early signal of potential harm to study participants, which was studied through the off-treatment follow-up period which demonstrated reversibility of the findings.
Due to EudraCT system limitations, which EMA is aware of, 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

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	03 August 2017
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	Belgium: 3
Country: Number of subjects enrolled	Canada: 37
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	Finland: 14
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Iceland: 129
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Japan: 28
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	Portugal: 8

Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	Switzerland: 11
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United Kingdom: 158
Country: Number of subjects enrolled	United States: 645
Worldwide total number of subjects	1144
EEA total number of subjects	214

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)	201
From 65 to 84 years	943
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

8970 participants were screened. One patient in the CNP520 50 mg arm was mis-randomized and not included in Number started.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CNP520 50 mg

Arm description:

50 mg capsule taken orally once daily

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 administered orally once daily

Arm title	CNP520 15 mg

Arm description:

15 mg capsule taken orally once daily

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 15 mg administered orally once daily

Arm title	Placebo

Arm description:

Matching placebo to 15 and 50 mg CNP520 taken orally once daily

Arm type	Placebo
Investigational medicinal product name	Matching placebo of CNP520 50 mg or 15mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Placebo administered orally once daily

Number of subjects in period 1	CNP520 50 mg	CNP520 15 mg	Placebo
Started	455	233	456
Completed	0	0	0
Not completed	455	233	456
Consent withdrawn by subject	18	7	13
Physician decision	1	-	1
Study terminated by Sponsor	424	222	438
Adverse event, non-fatal	10	3	3
Technical problems	1	-	-
Protocol deviation	-	1	-
Lost to follow-up	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	CNP520 50 mg
Reporting group description:	
50 mg capsule taken orally once daily	
Reporting group title	CNP520 15 mg
Reporting group description:	
15 mg capsule taken orally once daily	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to 15 and 50 mg CNP520 taken orally once daily	

Reporting group values	CNP520 50 mg	CNP520 15 mg	Placebo
Number of subjects	455	233	456
Age Categorical Units: participants			
<=64	76	45	80
65-69	181	82	162
>70	198	106	214
Sex: Female, Male Units:			
Female	284	148	288
Male	171	85	168
Race/Ethnicity, Customized Units: Subjects			
Caucasian	416	213	422
Black	7	1	5
Asian	18	12	22
Native American	3	2	1
Pacific Islander	2	1	0
Other	4	2	0
Unknown	5	2	6
Baseline API Preclinical Composite Cognitive Battery (APCC)			
APCC 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=better cognitive performance.			
Units: scores on a scale			
arithmetic mean	74.6	75.8	74.9
standard deviation	± 6.68	± 6.81	± 7.16
Baseline Battery for Assessment of Neurological Status (RBANS)			
RBANS is a tool to detect/characterize neurocognitive dementia changes in 5 neurocognitive domains; scores are from 40-160 and higher scores=better cognitive functioning.			
Units: scores on a scale			
arithmetic mean	100.5	102.0	100.7
standard deviation	± 11.96	± 12.09	± 12.42
Baseline Clinical Dementia Rating Sum of Boxes (CDR-SOB)			
CDR-SOB measures cognition and functioning in 6 domains; scores are from 0-18 and higher scores			

indicate greater disease severity			
Units: scores on a scale			
arithmetic mean	0.19	0.16	0.14
standard deviation	± 0.389	± 0.358	± 0.358

Reporting group values	Total		
Number of subjects	1144		
Age Categorical Units: participants			
<=64	201		
65-69	425		
>70	518		
Sex: Female, Male Units:			
Female	720		
Male	424		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	1051		
Black	13		
Asian	52		
Native American	6		
Pacific Islander	3		
Other	6		
Unknown	13		
Baseline API Preclinical Composite Cognitive Battery (APCC)			
APCC 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=better cognitive performance.			
Units: scores on a scale			
arithmetic mean			
standard deviation	-		
Baseline Battery for Assessment of Neurological Status (RBANS)			
RBANS is a tool to detect/characterize neurocognitive dementia changes in 5 neurocognitive domains; scores are from 40-160 and higher scores=better cognitive functioning.			
Units: scores on a scale			
arithmetic mean			
standard deviation	-		
Baseline Clinical Dementia Rating Sum of Boxes (CDR-SOB)			
CDR-SOB measures cognition and functioning in 6 domains; scores are from 0-18 and higher scores indicate greater disease severity			
Units: scores on a scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	CNP520 50 mg
Reporting group description:	
50 mg capsule taken orally once daily	
Reporting group title	CNP520 15 mg
Reporting group description:	
15 mg capsule taken orally once daily	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to 15 and 50 mg CNP520 taken orally once daily	

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:

Time-to-event (TTE) was defined as the first confirmed diagnosis of MCI due to Alzheimer's disease (AD) or dementia due to AD (whichever occurred first). An event was identified when adjudication by the progression adjudication committee (PAC) was 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. Time to censoring date was calculated from day of randomization. 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 studies, only a small number of events following the above definition were observed.

End point type	Primary

End point timeframe:

Baseline to end of exposure for a maximum of 617 days (premature termination)

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	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	455	233	456	
Units: percentage of participants				
number (confidence interval 95%)				
Week 26 n=6,1,3	0.99 (0.96 to 1.00)	1.00 (0.999 to 99.999)	1.00 (0.97 to 1.00)	
Week 52 n=6,1,3	0.97 (0.94 to 0.99)	0.99 (0.92 to 1.00)	0.99 (0.96 to 1.00)	
Week 78 n=6,1,3	0.97 (0.94 to 0.99)	0.99 (0.92 to 1.00)	0.97 (0.88 to 0.99)	

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:

Baseline to Week 26, 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	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	455	233	456	
Units: Total scores				
arithmetic mean (standard deviation)				
Week 26 n=160,79,162	-3.1 (± 5.20)	-2.9 (± 5.00)	-1.7 (± 4.44)	
Last on-treatment n=269,144,275	-2.2 (± 4.88)	-0.8 (± 4.67)	-1.3 (± 5.21)	
Last off-treatment n=255,124,260	-0.8 (± 4.56)	-0.8 (± 4.38)	-0.8 (± 4.64)	

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:

Baseline to Week 26, Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	455	233	456	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 26 n=160,78,160	0.17 (± 0.606)	0.20 (± 0.451)	0.08 (± 0.385)	
Last on-treatment n=265,144,267	0.15 (± 0.557)	0.08 (± 0.449)	0.10 (± 0.468)	
Last off-treatment n=254,117,256	0.09 (± 0.525)	0.07 (± 0.401)	0.10 (± 0.565)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in the Total and 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:

Baseline to Week 26, Baseline to Last on-treatment and Baseline to Last-off treatment

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	455	233	456	
Units: scores				
arithmetic mean (standard deviation)				
Total Week 26 n=162,81,162	-5.8 (± 8.54)	-6.3 (± 8.58)	-3.4 (± 8.35)	
Total Last on-treatment n=356,183,353	-3.4 (± 8.66)	-3.5 (± 8.87)	-0.5 (± 8.88)	
Total Last off-treatment n=259,125,265	-1.3 (± 8.12)	-2.4 (± 9.55)	-1.9 (± 8.56)	
Immediate memory - Week 26 n=162,81,162	-9.8 (± 11.85)	-9.7 (± 12.10)	-5.2 (± 11.26)	
Immediate memory - Last on-treatment n=347,183,353	-5.9 (± 13.01)	-4.0 (± 13.54)	-1.1 (± 13.04)	
Immediate memory- Last off-treatment n=259,125,266	-3.1 (± 12.50)	-4.8 (± 13.52)	-3.0 (± 13.00)	
Visuospatial Week 26 n=162,81,162	-5.6 (± 15.11)	-5.4 (± 15.51)	-2.6 (± 15.26)	
Visuospatial Last on-treatment n=347,183,353	-3.7 (± 14.90)	-3.8 (± 15.14)	-1.2 (± 13.95)	
Visuospatial Last off-treatment n=259,125,266	-1.5 (± 14.87)	-0.7 (± 14.37)	-1.2 (± 14.56)	
Language Week 26 n=162,81,162	-0.8 (± 11.48)	-1.8 (± 11.05)	-3.1 (± 11.07)	

Language Last on-treatment n=347,183,353	-0.3 (± 11.95)	-1.7 (± 11.69)	-1.3 (± 12.58)	
Language Last off-treatment n=259,125,265	-1.0 (± 10.93)	-2.0 (± 12.68)	-3.4 (± 11.47)	
Attention Week 26 n=162,81,162	0.1 (± 11.19)	-0.1 (± 10.37)	0.1 (± 10.56)	
Attention Last on-treatment n=347,183,353	0.0 (± 11.30)	0.0 (± 10.68)	0.7 (± 10.99)	
Attention Last off-treatment n=259,125,265	1.6 (± 11.59)	1.7 (± 10.65)	1.1 (± 9.81)	
Delayed memory - Week 26 n=162,81,162	-5.5 (± 11.54)	-5.0 (± 11.68)	-2.1 (± 11.69)	
Delayed memory - Last on-treatment n=346,183,353	-3.0 (± 11.58)	-2.8 (± 10.56)	0.8 (± 11.43)	
Delayed memory - Last off-treatment n=259,125,265	-1.0 (± 10.91)	-2.5 (± 10.34)	-0.5 (± 10.57)	

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:

Baseline to Week 26, Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	455	233	456	
Units: Total scores				
arithmetic mean (standard deviation)				
Week 26 n=155,78,157	0.9 (± 7.90)	0.2 (± 5.52)	0.5 (± 6.76)	
Last on-treatment n=266,143,268	1.6 (± 8.03)	0.4 (± 5.62)	0.7 (± 8.25)	
Last off-treatment n=249,122,255	-0.1 (± 6.49)	0.0 (± 7.02)	0.1 (± 7.47)	

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.

End point type	Secondary

End point timeframe:

Baseline to Week 26, Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	455	233	456	
Units: Total scores				
arithmetic mean (standard deviation)				
Week 26 n=153,76,153	-0.3 (± 7.55)	1.7 (± 7.77)	-1.2 (± 6.10)	
Last on-treatment n=252,138,255	0.5 (± 7.58)	0.7 (± 8.49)	0.2 (± 7.00)	
Last off-treatment n=223,113,239	0.5 (± 6.97)	0.0 (± 6.74)	1.2 (± 9.36)	

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) and a general assessment of brain abnormalities.

End point type	Secondary

End point timeframe:

Baseline up to study termination approximately 617 days

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	455	233	456	
Units: participants				
Presence of ARIA-H	0	0	0	
Questionable presence of ARIA-E	1	0	2	

White matter disease worsening: 1-3 increase	4	2	3	
White matter disease worsening: 4- - >8 increase	0	0	0	
White matter disease worsening >8	0	0	0	
Any other MRI abnormalities	1	0	1	

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): hippocampus, lateral ventricles, and total brain. 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:

Baseline to Week 26, Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	455	233	456	
Units: Percentage of volume change				
arithmetic mean (standard deviation)				
Week 26 n=169,83,169	-1.1016 (± 1.03196)	-0.9348 (± 0.85477)	-0.5552 (± 1.21385)	
Last on-treatment n=179,85,182	-1.0427 (± 0.93751)	-0.9205 (± 0.75633)	-0.5378 (± 1.09542)	
Last off-treatment n=72,44,81	-0.6984 (± 0.73644)	-0.9188 (± 0.94516)	-0.5811 (± 0.75412)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in 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 Week 26, Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	97	49	90	
Units: ng/mL				
arithmetic mean (standard deviation)				
AB40 Last on-treatment n=1,0,1	-7.320 (± 999.9)	999.9 (± 999.9)	-0.760 (± 999.9)	
AB40 Last off-treatment n=16,5,13	-1.492 (± 1.9263)	0.804 (± 1.9220)	-1.172 (± 1.7408)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in 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 Week 26, Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	48	90	
Units: pg/mL				
arithmetic mean (standard deviation)				
AB42 Last on-treatment n=1,0,1	-366.200 (± 999.9)	999.9 (± 999.9)	-61.300 (± 999.9)	
AB42 Last off-treatment n=16,5,13	20.431 (± 74.5595)	-68.660 (± 62.8505)	21.246 (± 104.3395)	

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 CNP520 vs placebo on Alzheimer’s Disease-related biomarkers

End point type	Secondary

End point timeframe:

Baseline to Months 24 and 60

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	0[4]	0[5]	
Units: standardized uptake ratio				
number (not applicable)				

Notes:

[3] - No available data

[4] - No available data

[5] - No available data

Statistical analyses

No statistical analyses for this end point

Secondary: Change in amyloid deposition as measured by standardized uptake ratio (SUVR) of positron emission tomography (PET) scan with amyloid radiotracer

End point title	Change in amyloid deposition as measured by standardized uptake ratio (SUVR) of positron emission tomography (PET) scan with amyloid radiotracer

End point description:

To demonstrate the effects of CNP520 vs placebo on Alzheimer’s Disease-related biomarkers

End point type	Secondary

End point timeframe:

Baseline to Months 24 and 60

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[6]	0[7]	0[8]	
Units: standardized uptake ratio				
number (not applicable)				

Notes:

[6] - Only baseline amyloid PET scans are available

[7] - Only baseline amyloid PET scans are available

[8] - Only baseline amyloid PET scans are available

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CSF levels of total tau and phosphorylated tau

End point title	Change in 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 Week 26, Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	49	92	
Units: pg/mL				
arithmetic mean (standard deviation)				
Total tau - Last on-treatment n=1,0,1	40.000 (± 999.9)	999.9 (± 999.9)	-12.600 (± 999.9)	
Total tau - Last off-treatment n=16,5,13	-22.119 (± 28.6218)	-3.320 (± 21.1548)	-3.238 (± 23.4442)	
Phosphorylated tau - Last on-treatment n=1,0,1	-2.360 (± 999.9)	999.9 (± 999.9)	-0.550 (± 999.9)	
Phosphorylated tau - Last off-treatment n=16,5,13	-1.849 (± 2.3397)	-0.852 (± 2.7005)	0.065 (± 1.3032)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Neurofilaments

End point title	Change in 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, Baseline to Last on-treatment and Baseline to Last off-treatment

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226	103	230	
Units: pg/mL				
arithmetic mean (standard deviation)				
Week 26 n=33,17,38	0.622 (± 4.5576)	0.901 (± 4.6732)	-5.731 (± 40.9042)	
Last on-treatment n=33,15,40	0.932 (± 4.2494)	0.041 (± 3.4144)	-5.771 (± 39.8254)	
Last off-treatment n=5,2,1	-2.764 (± 3.0981)	7.350 (± 9.5884)	3.880 (± 999.9)	

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 up to study termination approximately 617 days

End point values	CNP520 50 mg	CNP520 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	455	233	456	
Units: events				
Any suicidal ideation n=13,3,9	25	6	12	
Any suicidal behavior n=1,0,1	1	999	1	

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 until end of study treatment plus 31 days of washout period for a maximum duration of 617 days.	
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	CNP520 50 mg
Reporting group description:	
CNP520 50 mg	
Reporting group title	CNP520 15 mg
Reporting group description:	
CNP520 15 mg	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	CNP520 50 mg	CNP520 15 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 455 (3.30%)	9 / 233 (3.86%)	15 / 456 (3.29%)
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)			
Basal cell carcinoma			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (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
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (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
Breast cancer			

subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chordoma			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (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
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (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
Hypertension			

subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (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
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serum ferritin decreased			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
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	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (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
Radius fracture			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (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
Subdural haematoma			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic lung injury			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (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
Coronary artery disease			
subjects affected / exposed	2 / 455 (0.44%)	1 / 233 (0.43%)	0 / 456 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (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

Supraventricular tachycardia			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (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
Seizure			

subjects affected / exposed	1 / 455 (0.22%)	1 / 233 (0.43%)	0 / 456 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
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	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (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
Pancreatitis			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (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
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 455 (0.00%)	0 / 233 (0.00%)	1 / 456 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 455 (0.00%)	1 / 233 (0.43%)	0 / 456 (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
Osteoarthritis			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (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
Pneumonia influenzal			
subjects affected / exposed	1 / 455 (0.22%)	0 / 233 (0.00%)	0 / 456 (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

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

Non-serious adverse events	CNP520 50 mg	CNP520 15 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 455 (30.11%)	62 / 233 (26.61%)	89 / 456 (19.52%)
Investigations			
Weight decreased			
subjects affected / exposed	19 / 455 (4.18%)	3 / 233 (1.29%)	7 / 456 (1.54%)
occurrences (all)	19	3	7
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	11 / 455 (2.42%)	7 / 233 (3.00%)	5 / 456 (1.10%)
occurrences (all)	14	7	6
Nervous system disorders			
Dizziness			

subjects affected / exposed	14 / 455 (3.08%)	7 / 233 (3.00%)	8 / 456 (1.75%)
occurrences (all)	16	7	8
Headache			
subjects affected / exposed	12 / 455 (2.64%)	8 / 233 (3.43%)	15 / 456 (3.29%)
occurrences (all)	13	9	16
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	32 / 455 (7.03%)	12 / 233 (5.15%)	16 / 456 (3.51%)
occurrences (all)	40	15	18
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	18 / 455 (3.96%)	7 / 233 (3.00%)	3 / 456 (0.66%)
occurrences (all)	19	7	3
Anxiety			
subjects affected / exposed	21 / 455 (4.62%)	4 / 233 (1.72%)	8 / 456 (1.75%)
occurrences (all)	23	5	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 455 (2.42%)	6 / 233 (2.58%)	11 / 456 (2.41%)
occurrences (all)	14	6	13
Back pain			
subjects affected / exposed	14 / 455 (3.08%)	2 / 233 (0.86%)	4 / 456 (0.88%)
occurrences (all)	14	2	4
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 455 (1.32%)	7 / 233 (3.00%)	4 / 456 (0.88%)
occurrences (all)	6	7	4
Nasopharyngitis			
subjects affected / exposed	22 / 455 (4.84%)	9 / 233 (3.86%)	11 / 456 (2.41%)
occurrences (all)	27	11	11
Upper respiratory tract infection			
subjects affected / exposed	18 / 455 (3.96%)	5 / 233 (2.15%)	16 / 456 (3.51%)
occurrences (all)	19	6	17
Urinary tract infection			
subjects affected / exposed	8 / 455 (1.76%)	8 / 233 (3.43%)	7 / 456 (1.54%)
occurrences (all)	13	8	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 November 2017	Updated from GLP embryo-fetal development studies : CNP520 was not genotoxic nor teratogenic therefore male contraception was no longer required. Updated: a pooled concentration-effect analysis of ECG QT data from Phase 1 and Phase 2a studies, revealed that there was no relevant QT prolongation by CNP520 and therefore concomitant medications associated with Torsades de Pointes were allowed. Included tau PET at screening, month 24 and month 60, to assess neurofibrillary tangles burden as a secondary endpoint.
18 December 2018	This amendment primarily addressed proactive actions required to enhance the ongoing monitoring of CNP520. The changes to the protocol were required to reflect the USM action plan from 13 Nov 2018: an additional cognitive assessment with RBANS at the 3 Month visit, as well as the NPI-Q at 3 and 6 months and every 6 months thereafter was added. Other changes to the protocol included: Potential lower dose regimen options targeting less than 60% reduction of CSF Aβ. Such dose regimen modification (DRM process) could be activated upon DMC recommendation after review of CNP520 data and/or in light of new data on either CNP520 or other BACE inhibitors. Incorporation of changes required by local health authorities and clarifications of different administrative aspects of the protocol.
07 January 2020	Modified treatment epoch (period)completion (TEC) visit • The following assessments were no longer required: MRI, PET and lumbar puncture for CSF samples. 2. Modified end of study visit: • Timing was changed from 3 Month post TEC visit to 6 Month post TEC visit: Simplified assessments required at this visit included: AEs and SAEs, RBANS, CDRSOB, volumetric MRI, blood sample for biomarkers.

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, which EMA is aware of, 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: