2016-002976-28

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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)

To evaluate the efficacy and safety of CNP520 in participants at risk for the onset of clinical symptoms of Alzheimer’s Disease (AD)

CCNP520A2202J

v03

2020-01-07

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Novartis Pharma AG

Lichtstrasse 35

Basel

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Novartis Pharma Arzneimittel GmbH

Roonstrasse 25

Nürnberg

D-90429

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Novartis Pharma AG

Lichtstrasse 35

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Clinical Trial Information Desk

Novartis Pharma AG

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Parexel International Romania s.r.l.

89-97 Grigore Alexandrescu St.

Bucharest

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Novartis Pharma B.V.

Haaksbergweg 16

Amsterdam

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CNP520 15 mg

CNP520

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CNP520 is an orally active beta-secretase (BACE-1) inhibitor

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CNP520 50 mg

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CNP520 is an orally active beta-secretase (BACE-1) inhibitor

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CNP520

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PR1

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Pregelatinized starch, microcrystalline cellulose, magnesium stearate. 
Capsule - gelatin, titanium oxide, iron oxide, red/Ferric oxide.

PR2

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Pregelatinized starch, microcrystalline cellulose, magnesium stearate. 

Capsule - gelatin, titanium oxide, iron oxide, red/Ferric oxide.

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PR1

PR2

PL1

Novartis Pharma Arzneimittel GmbH

Roonstrasse 25

Nürnberg

D-90429

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Alzheimer's disease

Dementia

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Alzheimer's disease

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- To demonstrate the effect of CNP520 vs placebo on time to diagnosis of MCI due to AD or dementia due to AD, whichever occurs first during the course of the study.
- To demonstrate the effect of CNP520 vs placebo on cognition using APCC.

Key secondary objective:□
- To demonstrate the effects of CNP520 vs placebo on global clinical status.□
Secondary objectives:□
- To demonstrate the safety and tolerability of CNP520 vs placebo.□
- To demonstrate the effects of CNP520 vs placebo on cognition using Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).□
- To demonstrate the effects of CNP520 vs placebo on function.□
- To demonstrate the effects of CNP520 vs placebo on Magnetic Resonance Imaging (MRI) measures suggestive of cerebral amyloid angiopathy (CAA).□
- To demonstrate the effects of CNP520 vs placebo on brain atrophy.□
- To demonstrate the effects of CNP520 vs placebo on AD-related biomarkers.

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Screening part I: Participants eligible for inclusion must fulfill all of the□
following criteria prior to scheduling the genetic disclosure.□
1. Written informed consent must be obtained before any assessment is□
performed as part of the study, including consent to receive disclosure of□
their risk estimates to develop clinical symptoms of AD based on their□
APOE genotype and, if HTs, with evidence of elevated brain amyloid.□
2. Male or female, age 60-75 years inclusive, at the time of signing the□
informed consent. To ensure that no more than 20% of participants in the age group 60-64 years are randomized across the whole recruitment□
period, a site level process will be implemented.□
3. Females must be considered post-menopausal and not of child bearing□
potential i.e. they have had 12 months of natural (spontaneous)□
amenorrhea with an appropriate clinical profile (e.g. history of□
vasomotor symptoms), or have had surgical bilateral oophorectomy□
(with or without hysterectomy), total hysterectomy, or tubal ligation.□
4. Intellectually, visually and auditorily capable, fluent in, and able to□
read, the language in which study assessments are administered (e.g.□
completion of at least 6 years of regular schooling or sustained□
employment or equivalent local level of knowledge).□
5. Mini-Mental State Examination total score ≥24.□
6. Willing to have a study partner throughout the study.□
Screening part II: Participants eligible for inclusion must fulfill all of the□
following criteria prior to randomization based on the results from the□
screening test procedures.□
7. Carrier of at least one ε4 allele of the APOE gene: HMs with elevated□
or not elevated brain amyloid OR HTs with elevated brain amyloid (as□
measured in CSF collected via lumbar puncture or by amyloid PET□
imaging).□
Note: In cases where both lumbar puncture (CSF) amyloid and amyloid□
PET imaging tests are performed, at least one should be indicative of□
elevated brain amyloid.□
8. Cognitively unimpaired at screening visit as defined by: Score of 85 or□
greater on the RBANS delayed memory index score AND CDR global□
score of 0 with two special exceptions: a) If the RBANS delayed memory□
index score is between 70 and 84 (inclusive) AND the global CDR = 0,□
the participant may be allowed to continue ONLY if the investigator□
judges that cognition is unimpaired following review of the□

MCI/dementia criteria; b) If the global CDR score = 0.5 AND the RBANS□
delayed memory index score is 85 or greater, the participant may be□
allowed to continue ONLY if the investigator judges that cognition is□
unimpaired following review of the MCI/dementia criteria.□
9. Having a study partner who agrees to participate in the study and who□
is intellectually, visually, and auditorily capable, and fluent in, and able□
to read, the language in which study assessments are administered.□
Additionally, the study partner must be capable of and willing to: a)□
Accompany the participant to visits that requires the input of the study□
partner; b) Meet the definition of a "study partner".□
Other protocol defined inclusion criteria may apply.

Screening part I: Participants will be excluded if they fulfill any of the□
following criteria prior to scheduling the genetic disclosure.□
1. Current medical or neurological condition that might impact cognition□
or performance on cognitive assessments e.g. MCI, dementia,□
Huntington's or Parkinson's disease etc.□
2. Advanced, severe progressive or unstable disease that may interfere□
with the safety, tolerability and study assessments, or put the□
participant at special risk e.g. active hepatitis, HIV infection, severe□
renal impairment, severe hepatic impairment etc.□
3. History of malignancy of any organ system, treated or untreated,□
within the past 60 months, regardless of whether there is evidence of□
local recurrence or metastases. However, localized nonmalignant tumors□
not requiring systemic chemo- or radio-therapy, localized basal or□
squamous cell carcinoma of the skin, in-situ cervical cancer are□
permitted.□
4. Current treatment with Cholinesterase Inhibitors and/or another AD□
treatment.□
5. Clinically relevant depigmenting or hypopigmenting conditions or□
active/history of chronic urticaria in the past year.□
6. Score "yes" on item 4 or 5 of the Suicidal Ideation section of the□
eCSSRS patient-reported outcome, if this ideation occurred in the past 6□
months, or "yes" on any item of the Suicidal Behavior section, except for□
the "Non-Suicidal Self- Injurious Behavior", if this behavior occurred in□
the past 2 years prior to screening.□
7. Lacking psychological readiness to receive APOE genotype/amyloid□
status results, as assessed based on investigator's judgement supported□
by the pre-disclosure rating scales: Geriatric Depression Scale total score□
>6; Six Item Subset Inventory of the modified State Trait Anxiety□
Inventory total score >17.□
8. Use of other investigational drugs prior to screening until: Small□
molecules: after 5 half-lives, or within 30 days until the expected□
pharmacodynamic effect has returned to baseline, whichever is longer;□
Biologicals: blood concentration has returned to baseline (or below□
serological responder threshold) for antibodies induced by active□
immunotherapy; or 5 half-lives for monoclonal antibodies or other□
biologicals.□
9. Treatment□
a) in the 4 weeks prior to randomization with any drug or treatment□
known for the potential to cause major organ system toxicity i.e. drugs□
that may require periodic safety monitoring of a specific organ or body□
fluid.□

b) in the 4 weeks prior to randomization and/or current treatment with□
any CNS active drugs with the exceptions.□
10. Current chronic treatment (>3 months) with: Strong CYP3A4□
inducers or inhibitors; Drugs with a narrow therapeutic index known to□
be primarily metabolized by CYP2C or CYP3A isoenzymes and sensitive□
P-gp substrates.□
11. Violations of concomitant medication restrictions.□
12. Donation or loss of 400 mL or more of blood within 8 weeks prior to□
screening blood sampling and/or lumbar puncture if applicable.□
13. Contraindication or intolerance to MRI investigations.□
Screening part II: Participants fulfilling any of the following criteria□
based on results from the screening test procedures will be excluded.□
14. A positive drug screen, if, in the investigator's opinion, this is due to□
drug abuse. Participants with a positive drug screen not believed to be□
related to drug abuse can be re-screened.□
15. Previous participation in a CNP520 study with >3-month exposure to□
active treatment.□
16. Significantly abnormal laboratory results at screening, meeting the□
exclusionary alert values specified in the Laboratory Manual. If, in the□
opinion of the investigator, an abnormal finding is the result of a□
temporary condition, the laboratory test can be repeated.□
17. Current significant ECG findings from central reader that are□
assessed as clinically significant by the investigator. QTc interval >500□
ms is exclusionary.□
18. Brain MRI results from the central reading showing findings□
unrelated to AD that, in the opinion of the investigator might be a□
leading cause of future cognitive decline, might pose a risk to the□
participant, or might confound MRI assessment for safety monitoring□
(e.g. extensive white matter lesions, stroke, cerebrovascular disease as□
evidenced by multiple lacunar infarcts ≤20 mm or single infarct >20 mm,□
evidence of cerebral contusion etc.).□
19. If PET scans are scheduled for this participant: Total dosimetry□
above the acceptable exposure in the country when combining the□
previous or planned Nuclear Medicine Radiology exposure and the□
scheduled study PET scan(s).□
20. If CSF sampling is scheduled for this participant: Contraindication to□
lumbar puncture e.g. low platelet count, abnormal prothrombin time□
international normalized ratio, history of back surgery (except□
microdiscectomy or laminectomy over one level), signs or symptoms of□
intracranial pressure etc.□
Other protocol defined exclusion criteria may apply.

- Time to the first event with event defined as the first confirmed diagnosis of MCI due to AD or dementia due to AD.□
- Change from baseline to month 60 in APCC score.

- Baseline to month 60.□
- Baseline to month 60.

- Change from baseline to month 60 in Clinical Dementia Rating Scale - Sum of Boxes (CDRSOB) score.
- Frequencies, changes from baseline, Kaplan-Meyer estimates when applicable of: Adverse events; Skin events based on a centralized dermatological monitoring; Safety findings from brain structural MRI central reader; Laboratory tests; Vital signs; ECG findings; Prospective suicidality assessment (ideation and behavior) from eC-SSRS.
- Change from baseline to month 60 in total RBANS score and individual neurocognitive domain index scores.
- Change from baseline to month 60 in total score of the Everyday Cognitive (ECog) scale: ECogsubject and ECog-informant.
- Number, intensity and location of microhemorrhages and white matter hyperintensities using the Wahlund scale, both as assessed by central MRI reader.
- Change from baseline to month 60 on volume of brain regions as measured by volumetric MRI.
- Change from baseline to 24 and 60 months on: amyloid deposition as measured by standardized uptake ratio (SUVR) of radiotracer positron emission tomography (PET) scan; CSF levels of Aβ40, Aβ42; neurodegeneration as measured by CSF levels of total tau and
phosphorylated tau. Collected only in participants who consented to additional voluntary procedures.

- Baseline to month 60.
- Baseline to month 60.
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Participants at risk for the onset of clinical symptoms of AD

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Upon study completion (assuming futility was not met), participants may have the opportunity to enter an extension under a separate study, if eligible.

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Cronenburg 2

Amsterdam

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Brain Research Center Den Bosch

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Receipt of batch samples from centres/shipment to reference labs; sample analysis; lab supplies

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Assay validation/transfer; sample analysis

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Site training; CRF/data review; central reading/image analysis/archiving of MRI and Tau PET scans

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Central dermatology, photography, monitoring & review; training

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Supply of Amyloid PET ligand (flutemetamol) to various sites in various countries

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Amyloid/Tau biomarker supply/expertise; PET reading/analysis/archiving; CRF/data review; training

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Training; reading/archiving re:scales/MCI&AD diagnosis; adjudication;eSource data collection

Parexel International GmbH

CTRS-PL

Klinikum Westend, Haus 18, Spandauer Damm 130

Berlin

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Regional warehousing/auxiliary labelling

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Regional warehousing/auxiliary labelling

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Regional warehousing/auiliary labelling

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Subject randomization management; Drug supply management; IRT services

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Long term Sample storage and shipments

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Protocol, analysis plan & IDMC review; SAE programming & SAE narratives; IDMC reports & liaison

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Implementation and management of study website; Management of site recruitment tools; Travel support

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Rental of -70 freezer to BRC Den Bosch

Central Committee on Research Involving Human Subjects (CCMO)

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van der Boechorststraat 7

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