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

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Primary objectives: * To demonstrate the effects of CAD106 and CNP520, respectively, vs. placebo on Time-to-event (TTE), with event defined as a diagnosis of MCI due to AD or dementia due to AD, whichever occurs first during the course of the study...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Structural brain disorders
Study type	Interventional

Summary

ID

NL-OMON50176

Source
ToetsingOnline

Brief title
CAPI015A2201J

Condition

- Structural brain disorders

Synonym
Alzheimer disease; Dementia

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: APOE4 Homozygotes, preclinical Alzheimer□s Disease (AD) A□ lowering

Outcome measures

Primary outcome

Time-to-event (TTE) endpoint and the APCC score

Secondary outcome

CDR-SOB, ECog, individual scales included in APCC and RBANS, PET, Volumetric

MRI, Total tau, tau in CSF

Study description

Background summary

Alzheimer*s disease (AD) is one of the most prevalent neurological disorders worldwide and the most common and debilitating age-related condition, causing progressive amnesia, dementia, and ultimately global cognitive failure and death. Currently, the only pharmacological therapies available are symptomatic drugs such as cholinesterase inhibitors (ChEIs) or other drugs used to control the secondary behavioral symptoms of AD.

Study objective

Primary objectives:
* To demonstrate the effects of CAD106 and CNP520, respectively, vs. placebo on Time-to-event (TTE), with event defined as a diagnosis of MCI due to AD or dementia due to AD, whichever occurs first during the course of the study.
* To demonstarte the effects of CAD106 and CNP520, respectively, vs. placebo on cognition as measured by the change from Baseline to Month 60 in the APCC test

score.

Study design

This study protocol has multiple epochs with two informed consents required:
* Pre-screening Epoch and Genetic Disclosure Follow-up (Informed consent #1);
* Screening, Treatment and Follow-up Epochs (Informed consent #2).
The Pre-screening Epoch includes pre-screening assessments for evaluation of disclosure of APOE genotype to patients; the Genetic Disclosure Follow-up includes assessment telephone calls for all participants who received disclosure of their genotype.
The Treatment Epoch follows a randomized, double-blind, placebo-controlled, two-cohort parallel group design in which participants receive the investigational treatments or their matching placebo for at least 60 months.

Intervention

Cohort I (CAD106 and placebo):
Arm #1: CAD106 450 µg + Alum 450 µg given i.m.
Arm #2: Placebo to CAD106 + Alum 450 µg given i.m.

Cohort II (CNP520 and placebo):
Arm #3: CNP520 capsule p.o. for once daily administration at the dose determined prior to initiation of Cohort II.
Arm #4: Placebo to CNP520 p.o.

Study burden and risks

See schedule of activities in protocol. Patients will have following procedures for the study:
APOE genotype
Blood sampling
Physical/neurological/skin assessment
ECG
MRI
PET-scan
Skin images for central dermatology review in case of findings at skin assessment

Patients will also (have) complete questionnaires and keep an eDiary. The diary will be complete for 7 days after the first five injections (baseline, week 7, 13, 26 and 39) and thereafter yearly in week 52, 104, 156 and 208.

Possible side effects CAD106
- Symptoms or reactions to the injection place that are comparable with those after a flu injection

- Pain and redness of the skin
- Allergically skin rash distributed over the body and in the neck
- Amyloid Related Imaging Abnormalities (1 incident of ARIA-E in previous study)
Possible side effects CNP520:
- Skin reactions (mainly itching)
Possible side effects study procedures
CSV samples:
-light itching feeling, pain and/or pressure
- Headache
- a light feeling in the head or dizziness
- Infection
- Bleedings in the brain
- swelling of the brain
MRI (with or without contrast agent):
- *Enclosed* (claustrophobic) feeling
- Cannot be done in case of pregnancy or if metal objects in the body
MRI with contrast agent (if signs of infection):
- Nausea
- Pain, warm feeling, swelling, blue spot
- Small blood clot or infection on the injection place
- Skin rash or other signs of allergy
- rare disease where some of your body parts get scarred
Amyloïd-PET-scan
- *Enclosed* (claustrophobic) feeling
- allergic
- fainting, or pain, swelling, a blue spot, a small blood clot or infection on the place of injection
- headache
- musculoskeletal pain
- high blood pressure
- nausea
- fatigue
- reaction on the place of injection
- maximum radiation during one PET-procedure is 6-8 mSv.

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Pre-screening Epoch and Genetic Disclosure Follow-up inclusion criteria1.
Written informed consent (Informed consent #1) obtained before any assessment is performed, including consent to receive disclosure of their APOE genotype.
2. Male or female, age 60 to 75 years inclusive, at the time of signing the informed consent #1 (same age restriction also applied at informed consent #2).
a. Once the cap of approximately 20% of total participants in the age group 60-64 years is met, a restriction to this age group will apply.
3. Females must be considered post-menopausal and not of child bearing potential. Confirmation will be obtained for those who continue on to the Screening Epoch.
4. Mini-Mental State Examination (MMSE) total score * 24 (can be based on documented result obtained i previous 3 months).
5. Psycholgical readiness to receive APOE genotype information based on pre-disclosure rating scales:
a. Geriatric Depression Scale (GDS short form) total score *6.
If the score is between 7 and 10 (inclusive), the participant can only be included based on investigator*s judgment assessing in particular the scores of the questions:
i. Item 3: *Do you feel your life is empty?*
ii. Item 6: *Are you afraid that something bad is going to happen to you?*
iii. Item 12: *Do you feel pretty worthless the way you are now?*

iv. Item 14: *Do you feel your situation is hopeless?*
b. Six Item Subset Inventory of the STAI-AD total score *17.
If the score is 18 or 19, the participant can only be included based on the investigator*s judgment.
6. Participant is fluent in, and able to read the language in which the study are administered (e.g. completion of at least 6 years of regular schooling or sustained employment).
7. Participant*s willingness to have a study partner for the Screening and Treatment epoch.
Screening and Treatment Epoch inclusion criteriaParticipants eligible for inclusion must fulfill all of the following criteria prior to randomization:
1. Written informed consent (Informed consent #2) for participation to the Screening and Treatment Epochs (participant must still be between 60-75 years, inclusive at the time of signing ICF #2; respectively 65-75 after reaching the maximum of 20% in the ypunger age group 60-64).
2. Continue to meet all eligibility criteria from Pre-screening Epoch and Genetic Disclosure Follow-up, as confirmed by the review of the medical records by the Investigator.
3. Homozygous APOE4 genotype.
4. Cognitively unimpaired as defined by:
* At the screening visit, score of 85 or greater on the RBANS delayed memory index score
AND
* CDR global score of 0
with two exceptions:
If the RBANS delayed memory index score is between 70 and 84 (inclusive) AND the global CDR score <= 0, the participant may be allowed to continue ONLY if the Investigator judges that cognition is unimpaired following review of the MCI/dementia criteria.
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.I
5. 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. age appropriate, history of vasomotor symptoms),) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before the amyloid PET.
Other protocol defined inclusion criteria may apply.
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Exclusion criteria

Pre-screening Epoch and Genetic Disclosure Follow-up exclusion criteria1. Any

disability that may prevent the participants from completing all study requirements (e.g., blindness, deafness, severe language difficulty).
2. Current medical or neurological condition that might impact cognition or performance on cognitive assessments.
3. Advanced, severe progressive or unstable disease that may interfere with the safety, tolerability and study assessments, or put the participant at special risk.
4. 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, localized vulvar carcinoma and localized prostate carcinoma with no progression over the past two years are permitted.
5. History of hypersensitivity to any of the investigational drugs or their excipients/adjuvant, or to drugs of similar chemical classes.
6. Indication for or current treatment with ChEIs and/or another AD treatment (e.g. memantine).
7. Contraindication or intolerance to MRI or PET investigations.Screening and Treatment Epoch exclusion criteria
Participants fulfilling any of the following criteria prior to randomization will be excluded.
Participants, who fulfill one or more exclusion criteria due to a temporary condition, or the use of treatment requiring a specific time window prior to randomization, can be re-screened at a later stage:
1. 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.For Cohort I (CAD 106) only, in addition, evidence of ARIA-H as demonstrated by:
* More than four cerebral microhemorrhages (defined as diameter * 10 mm on T2* sequence) regardless of their anatomical location
* Single area of superficial siderosis of the CNS or evidence of a prior cerebral macrohemorrhage (> 10 mm diameter)
2. Score *yes* on item four or item five of the Suicidal Ideation Section of the C-SSRS if this ideation occurred in the past six months, or *yes* on any item of the Suicidal Behavior Section, except for the *Non-Suicidal Self-Injurious Behavior* (item also included in the Suicidal Behavior Section) if this behavior occurred in the past two years prior to screening.
3. A positive drug screen at Screening, 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 (e.g. presence of prescription drugs in urine without evidence of prescription drug abuse), can be re-screened once.
4. Significantly abnormal laboratory results at Screening as described in appendix 13.4 or 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 once.

5. Clinically significant active infection which has not resolved wiothin 2 weeks prior to initial dosing.
6. Current clinically significant ECG findings (e.g. sustained ventricular tachycardia, significant second or third degree atrioventricular block without a pacemaker, prolonged QT syndrome).
7. Use of other investigational drugs prior to screening until:
* Blood concentration has returned to Baseline (or below Serological responder treshold) for biologics, e.g. monoclonal antibodies or antibodies induced by active immunotherapy; or
* Within 30 days or 5 half-lives, whichever is the longest for monoclonal antibodies or small molecules e.g. BACE-1 inhibitors.
8. Treatment in the four weeks prior to randomization with any drug or treatment known for their potential to cause major organ system toxicity, i.e. drugs that may require periodic safety monitoring of a specific organ or body fluid (e.g. clozapine, tamoxifen).
9. Violations of concomitant medication restrictions as described in Table 5-3.
10. Donation or loss of 400 mL or more of blood within 8 weeks prior to screening blood sampling and/or lumbar puncture if applicable.
11. Previous or planned Nuclear Medicine Radiology exposure that will exceed the acceptable dosimetry exposure in the country, when adding the scheduled study PET scans or allergy to low doses of fluorinated radioligands.
12. For Cohort II only: Participants with depigmenting or hypopigmenting conditions or active/history of chronic urticaris in the past year.
13. For Cohort I only: Participants with previous organ transplantation or stem cell transplantation.Exclusion criteria for participation in the biomarker CSF sampling:
14. Contraindication to lumbar puncture, e.g. low platelet count, abnormal prothrombin time international normalized ratio (PT-INR), history of lumbar-spinal surgery (with the exception of microdiscectomy or laminectomy over one level), signs or symptoms of intracranial pressure, spinal deformities or other conditions.
Other protocol defined exclusion criteria may apply.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-02-2018
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	07-04-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-03-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-04-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	21-08-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-09-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-10-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-11-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-11-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-01-2018
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-02-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-03-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	02-07-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-09-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015□002715□15-NL
ClinicalTrials.gov	NCT02565511
CCMO	NL56038.000.16