NOVARTIS

Clinical Development

CAD106/CNP520

Clinical Trial Protocol CAPI015A2201J / NCT02565511

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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List of abbreviations

Aβ	Amyloid-beta
AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	Adverse Event
ALT	Alanine Aminotransferase
APCC	API Preclinical Composite Cognitive (Battery)
API	Alzheimer's Prevention Initiative
APOE	Apolipoprotein E
APOE4	Apolipoprotein E ε4 allele
APP	Amyloid Precursor Protein
ARIA	Amyloid Related Imaging Abnormalities
ARIA-E	Amyloid Related Imaging Abnormality-edema
ARIA-H	Amyloid Related Imaging Abnormality-hemorrhages
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical classification
AUC	Area Under the Curve
BACE	Beta-site-APP Cleaving Enzyme
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices- Germany)
BUN	Blood Urea Nitrogen
BSA	Body Surface Area
CAA	Cerebral Amyloid Angiopathy
CDR	Clinical Dementia Rating
CDR-SOB	Clinical Dementia Rating Sum of Boxes
CFR	US Code of Federal Regulations
ChEIs	Cholinesterase-Inhibitors
CIs	Confidence Intervals
CLIA	Clinical Laboratory Improvements Amendments
CMO	Chief Medical Office
CNAR	Censoring not at random
CNS	Central Nervous System
CPK	Creatine Phospho Kinase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
(e)C-SSRS	(electronic) Columbia Suicide Severity Rating Scale
CYP3A4/2C	Cytocchrome P450 3A4/2C
DDI	Drug-Drug-Interaction
DMC	Data Monitoring Committee
DMAG	Disclosure Monitoring Advisory Group
DMI	(RBANS) Delayed Memory Index
DNA	Deoxyribonucleic Acid
DOA	Direct Oral Anticoagulant
DRM	Dose Regimen Modification
DTI	Diffusion Tensor Imaging

DVF	Diagnostic Verification Form
ECG	Electrocardiogram
ECog	Everyday Cognition Scale
ECRF	Electronic Clinical Report Form
EDC	Electronic Data Capture
ELISA	Enzyme Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked ImmunoSpot
EoS	End of Study
FAS	Full Analysis Set
FDA	Food & Drug Administration
FDG	Fluorodeoxyglucose
FLAIR	Fluid-Attenuated Inversion Recovery
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GLP	Good Laboratory Practice
GRE	Gradient Echo
HA	Health Authorities
Hb	Hemoglobin
HbA1C	Glycated Hemoglobin
HBV/HCV	Hepatitis B virus/Hepatitis C virus
HIV	Human Immunodeficiency Virus
HMs	Homozygotes for APOE4
HTs	Heterozygotes for APOE4
non-HMs	non-Homozygotes, i.e. Heterozygotes or non-carriers
IA	Interim Analysis
i.m.	Intramuscular
IMI	(RBANS) Immediate Memory Index
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IES	Impact of Events Scale
IgG	Immunoglobulin G
IGT-AD	Impact of Genetic Testing for Alzheimer's Disease
IPW	Inverse Probability Weighting
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	Lactate Dehydrogenase
LDR	Lower Dose Regimen
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LOAD	Late Onset Alzheimer's Disease
LP	Lumbar Puncture
LSM	Least Square Means
MAP	Master Analysis Plan (referring to DMC)

MAR	Missing at Random
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
mEOS	Modified End of Study
MFAS	Modified Full Analysis Set
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed Model Repeated Measure
MMSE	Mini Mental State Examination
MNAR	Missing not at random
(v)(f)MRI	(volumetric)(functional)Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTEC	Modified Treatment Epoch Completion
NACC	National Alzheimer's Coordination Center
NFL	Neurofilaments Light-chain
NIA	National Institute of Aging
NOAEL	No Observed Adverse Effect Level
NCR(AD)	National Cell Repository (for Alzheimer Disease)
NPI-Q	Neuropsychiatric Inventory Questionnaire
NR	see SR/NR
NYHA	New York Heart Association
q.d.	Quoque die (once each day)
OC/RDC	Oracle Clinical/Remote Data Capture
p.o.	Oral (per os)
PAC	Progression Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamic
PEI	Paul Ehrlich Institute
PET	Positron Emission Tomography
Pgp	P-Glycoproteins
PH	Proportional Hazards
PI	Principal Investigator
PK	Pharmacokinetics
PPW	Premature Participant Withdrawal
PRO	Patient Reported Outcomes
PS	Propensity Score
PT-INR	Prothrombin Time-International Normalized Ratio
QOL-AD	Quality of Life in Alzheimer's disease
QTcF	Fridericia QT Correction Formula
RAS	Randomized Analysis Set
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
rCMRgl	regional Cerebral Metabolic Rate for glucose
REVEAL	Risk Evaluation & Education for Alzheimer's Disease
RNA	Ribonucleic Acid
ROI	Region of Interest
(e)SAE	(electronic) Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan

SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SR/NR	Serological Responders/ Serological Non-Responders
SSRI	Selective Serotonin Re-uptake Inhibitor
STAI-AD	State Trait Anxiety Inventory for AD
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUVR	Standardized Uptake Ratio
TBL	Total Bilirubin
TE	Target Engagement
TEC	Treatment Epoch Completion
TI	Therapeutic Index
T_{max}	Time of maximum concentration
TSH	Thyroid Stimulating Hormone
TTE	Time-To-Event
ULN	Upper Limit of Normality
USM	Urgent Safety Measure
UTE	Unsatisfactory therapeutic effect
VAS	Visual Analogue Scale
WBC	White Blood Cells
WHO	World Health Organization
γ-GT	Gamma-Glutamyl Transferase

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Cohort	A group of newly enrolled participants treated at a specific dose and regimen (i.e. treatment group) at the same time.
Control drug	Drug(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dose level	The dose of drug given to the participants (total daily or weekly etc.).
Enrollment	Point/time of participants entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Genetic disclosure	The participant will be referred to a genetic counselor or such equivalent according to the local regulations. The genetic counselor will access the individual genotype of the participant and verify the participant's willingness to receive information about their individual genotype. Where appropriate, the counselor will proceed with counseling using standardized apolipoprotein E (APOE) risk information and talking points across all sites, and disclose the genotype.
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US Code of Federal Regulations (CFR) 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not* include protocol-specified concomitant background therapies when these are standard treatments in that indication.
Ligand (also radio ligand)	A radioactive biochemical substance (substance that is radiolabeled) used for Positron Emission Tomography (PET) imaging. Also referred to as tracer or radiotracer.
Medication number	A unique identifier on the label of each investigational drug package.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/participants with established disease and in those with newly-diagnosed disease.
Personal data	Participant information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. These data include participant identifier information, study information and biological samples.
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Premature participant(s) withdrawal	Point/time when a participant exits from the study prior to the planned completion of all investigational treatment administration and/or assessments.
Pre-screening	Assessments performed prior to disclosure of genotype to the participant.

Randomization number	A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm assignment.
Investigational drug/ treatment/ Study medication	Any single drug or combination of drugs administered to the participants as part of the required study procedures; includes investigational drug(s), active drug run-ins or background therapy. Also referred to as Study medication.
Study/investigational treatment discontinuation	Point/time when a participant permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature participants withdrawal.
Study medication	See Investigational drug/treatment
Tracer /Radiotracer	See Ligand
Participant Number	A number assigned to each participant who enrolls into the study.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when the participant does not want to participate in the study any longer, and does not allow any further collection of personal data

Amendment 6 (7-Jan-2020)

Amendment rationale

This amendment documents, for completeness, the **changes regarding follow-up of participants after early termination of CNP520 according to the Investigator Notifications distributed between July and December 2019.**

This amendment also serves the purpose to document the trial termination after Cohort I early termination (Investigator letter from 23-Sep-2019).

The changes related to discontinuation of treatment with CNP520 in Cohort II were already formally communicated via an Urgent Safety Measure (USM) dated 11-Jul-2019 and two subsequent Follow-up notifications (dated 1-Aug-2019 and 12-Dec-2019) summarized below.

The USM (11-Jul-2019) was triggered by an unexpected, mild, early worsening that was observed in some measures of cognition in the active treatment arms following the assessment of unblinded data of CNP520 by the independent Data Monitoring Committee (DMC), during a planned data review on 26-June-2019. This finding led the Sponsors to discontinue assessment of CNP520 in the two Phase 2/3 studies in the Generation Program in July 2019. Additionally, volumetric MRI (whole brain and hippocampal volume) indicated increased volume loss on active treatment and greater mean body weight loss was observed at 26 weeks on both doses vs control group

In this communication, randomized participants were instructed to stop the study medication immediately (with confirmation of the last dose taken to be documented), and to return to the site to complete:

1. Modified Treatment Epoch Completion (TEC) visit 399.
    - The following assessments were no longer required: MRI, PET and Lumbar Puncture for CSF samples.
2. Modified End of Study visit 401 (mEOS):
    - Timing was changed from 3 month post Treatment Epoch Completion visit to 6 month post Treatment Epoch Completion visit:
    - Simplified assessments required at this visit included: AEs and SAEs, RBANS, CDR-SOB, volumetric MRI (3DT1 sequence only), blood sample for biomarkers.

The Follow-up #1 (1-Aug-2019) was issued as a clarification to the USM, to recommend that the full MRI scan and a lumbar puncture at mTEC visit be conducted as specified in protocol v05 in case of early study discontinuation. These assessments were expected to allow evaluation of potential markers associated with cognitive decline and/or imaging findings.

This letter also specified an Interim Telephone Check-in Point, to occur approximately 3 months after the mTEC visit. More clarity was provided with a revised Table of Assessments for the two visits in scope (mTEC and mEoS).

The Follow-up #2 (12-Dec-2019) was issued after an unblinded analysis of the available data from post-treatment assessments demonstrated reversal of the worsening in key measures of cognition after CNP520 treatment discontinuation. The analysis assessed data from visits conducted within 1 to 8 weeks after wash-out of CNP520. Treatment-related imbalances were still observed for body weight and brain volumes as measured by volumetric MRI. These volume changes are interpreted as primarily related to effects of CNP520 on the existing amyloid pathology.

Taking into account the new data on reversibility of cognitive decline after CNP520 discontinuation, scheduling constraints and burden to participants, the Sponsors concluded that cognitive and volumetric MRI assessments were no longer required at the mEoS visits. Assessments for adverse events, concomitant medications, eCSSRS and measurement of body weight during the mEoS visits remained unchanged.

Changes to the protocol for Cohort II only:

This protocol amendment documents the final set of cumulative modifications after the Cohort II USM Follow-up #2 notification.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Section 3.1.2.2: specified window for scheduling the mEoS within the 12 weeks following the last Treatment Epoch visit.
- Section 3.5 and 5.4: Additional post-treatment interim analysis after treatment termination
- Table 6-4: Assessment Schedule for visit 401 is modified accordingly. Two Cohort-specific tables for the Follow visit 401 are created for clarity.
- Section 6.2 and footnote 15 to Table 6-4: mEoS visit may be converted to phone call in case of logistical constraints. No eCSSRS or body weight to be collected in such case.
- Section 8.4 and 8.5: Specified responsibility of DMC monitoring of safety and PAC adjudication of progression for data obtained for participants on treatment

No changes will be applied to sections that were superseded by the early trial termination (eg. Section 5.5.14 Early Study Termination by the Sponsor, or Section 9 – Data Analysis: All changes to analyses related to the early termination of the study will be documented in the statistical analysis plan prior to unblinding the study).

IRBs/IECs

Only applicable for Cohort II

This amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities as an administrative update for completeness of documentation.

The changes described above as part of the Urgent Safety Measure (USM) dated 11-Jul-2019 and Follow-up Notification to Investigators 1-Aug-2019 were required to enhance monitoring of participant safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). The changes described as part of the Follow-up #2 Notification to Investigators dated 12-Dec-2019 reduced the monitoring described under USM based on the new unblinded data analyses to lessen participants' burden and should have been implemented prior to IRB/IEC approval upon receipt by Investigator of the corresponding Notifications.

The changes herein described affect the Informed Consent. The Follow-up #2 USM notification dated 12-Dec-2019, included Appendix 3 - Information for Study Participants. This information was to be shared verbally with ongoing participants that came for their scheduled mEoS visit on site (or during the phone contact if applicable) prior to local EC/IRB approval of the revised ICF addendum with the appropriate note made in the source documentation.

Note: No changes were implemented to Cohort I. The Early Termination was performed according to protocol.

Summary of previous amendments

To date, five global amendments and three local amendments to the original protocol have been released with their respective rationale described below:

Amended Protocol v05 (Dec-2018)

Amended Protocol v04.01DE (Apr-2018)

Amended Protocol v04 (Nov-2017)

Amended Protocol v03 (Jun-2017)

Amended Protocol v02.01DE (Apr-2017)

Amended Protocol v02.01UK (Mar-2017)

Amended Protocol v02 (Sep-2016)

Amended Protocol v01 (Oct-2015)

Amendment 5 (18-Dec-2018)

Amendment rationale

This amendment primarily addresses proactive actions required to enhance the ongoing monitoring of CNP520. The changes to the protocol are required to reflect the Urgent Safety Measure (USM) action plan from 13-Nov-2018. Other changes to the protocol include introduction of a lower dose regimen option, incorporation of changes required by local health authorities and clarifications of different administrative aspects of the protocol.

The USM was triggered by the data disclosed about two other BACE inhibitors indicating an increase in neuropsychiatric events and a decline in cognition starting following the first 3 to 6

months of treatment. The protocol is therefore amended to include an additional cognitive assessment with RBANS, as well as the NPI-Q, at the 3-month visit,

Results from studies of two other compounds with the same mechanism of action did not indicate a decline in cognitive performance or increase in neuropsychiatric events, making it difficult to know whether the negative effects reported for some of the other compounds are due to BACE inhibition *per se* or due to other properties of the drugs. The available data from other sponsors indicate that the early effects on cognition were found with doses of BACE inhibitors leading to at least 60% reduction of Aβ in CSF. The 50 mg once daily dose of CNP520 in this study achieves an 86% reduction of CSF Aβ.

In light of the new data from some other BACE inhibitor compounds, potential lower dose regimen options targeting less than 60% reduction of CSF Aβ, are being proposed for the Cohort II treatment arm. Such dose regimen modifications 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.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Changes to protocol based on Urgent Safety Measure (USM) dated 13-Nov-2018

This amendment follows a Letter to Investigators issued on November 13, 2018 and includes 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)

- Adding results from other BACE inhibitors (Section 1)
- Adding RBANS and NPI-Q at the 3-month visit
  - Section 6.4.3: RBANS Form D to be used for the 3-month visit.
  - Addition of Table 6-5: RBANS version by visit
  - Table 6-2: Update to Assessment Schedule for addition of RBANS and NPI-Q at month 3

Changes to protocol re: Dose Regimen Modification (DRM)

- Section 3.1: Description of potential Dose Regimen Modification (DRM) in Cohort II
- Section 3.1.2.2: Addition of DRM for Cohort II if DMC deems current dose of CNP520 50 mg once daily as unfavorable or decision from Sponsor to activate the DRM.
- Section 3.3: Rationale for potential Lower Dose Regimen (LDR) if DRM is activated
- Table 3-1: New table comparing current CNP520 dose and LDR doses
- Section 3.5: Clarification of frequency of DMC meetings and potential for DRM
- Section 3.6: Clarification on risks and benefits of CNP520
- Section 5.3: Treatment arms
- Section 8.4: DMC role in DRM

- Section 9:
  - Description of dose regimen and primary treatment arms for final primary analysis with or without DRM.
  - DRM added to regular DMC safety evaluation.
  - Discussion of potential impact of DRM on type-1 error rate added.
  - Discussion of potential impact of DRM on power and sample size added.

Other changes to protocol

Section 2.2; 2.3, 9.5: Addition of secondary analyses for blood $A\beta_{40}$, $A\beta_{42}$ and NFL; additional exploratory analyses for APOE genotyping (relationship between CNP520 concentrations (plasma and CSF), brain amyloid measurements and concordance between baseline CSF and PET results for elevated amyloid criteria

Section 3.1.1/Figure 3-1: Reduction of Genetic Disclosure follow-up visits for non-HMs, as per DMAG recommendation (obtained offline on 14 Aug 2018), endorsed by DMC on 06 Nov 2018

Section 3.1.2.1: Description on extension of 12-week time frame in screening epoch in case of logistical issue.

Section 4.1 and 4.2: Additional clarification, examples for eligibility criteria (prescreening and screening, respectively); specification of numbering to include “a” for prescreening criteria and “b” for screening criteria (not in track changes)

Section 5.1.2: Describing process and documentation to activate the DRM.

Section 5.1.3, 6.6.3.1: Clarification of PET tracer usage

Section 5.5.1: Clarification on participant numbering.

Section 5.5.2: Clarification on dispensing the investigation treatment.

Section 5.4; 5.5.9: Clarification for re-randomization for participants in case of cohort termination.

Section 5.5.4: Clarification of number of maximum doses of CAD106.

Section 5.5.5: Clarification of dose adjustments/interruptions of study treatment (if dose changes is warranted by sponsor/DMC)

Section 5.5.6: New section on Rescue Medication.

Section 5.5.8, Table 5-2 and Table 5-3: Clarification and additional examples to restricted and prohibited treatments, also reformatting to categorize by cohort.

Section 6.1, 6.3.2, and Table 7-1: Revision and clarification of reporting new condition during prescreening or screening as medical history or AE

Section 6.1.12; 6.3.1: New section on Information to be collected on prescreening failures with updated information (removed from Section 6.3.1)

Table 6-2: Additional of optional Week 7 check in visit (via telephone)

Section 6.2, Table 6-2: Year 2 amyloid PET change from mandatory to voluntary

Section 6.3.3: New section on Diagnostic Verification Form for assessment of unimpaired cognition at Screening.

Section 6.3.4: New section on Other screening considerations

Section 6.3.5: New section on Screening extension beyond 12 weeks

Section 6.4.2: Clarification on APCC repeat assessments

Section 6.5.1: Update on requirements on Health Care Professionals who can perform physical and neurological exams.

Section 6.5.4: Clarification on screening lab tests

Section 6.5.5: Clarification on ECG

Section 6.5.4.1: Addition of local measurement of CSF cell count in case of safety concern in participant.

Section 6.6.1.3: noted Completion of A-beta - and Q-beta-specific T-cell lymphocyte response

Section 6.6.3.2: Fluid biomarkers change from voluntary to mandatory

Section 6.5.8.1. Table 6-2: Dermatologic photographs moved from baseline to screening.

Section 7.2.1; 7.2.2: Paper SAE reporting updated to electronic (eSAE).

Section 7.7: Clarification of use of the short eC-SSRS self-assessment PRO version.

Section 8.4, 9.6: Ad Hoc meetings for DMC increase frequency as needed.

Section 9.5.3 and 9.6: Sub-group analysis for AD related biomarkers added in line with definition of Stage 1 classification in the Draft FDA guidance.

Section 10.2: Introduce a re-consent process for participants who progressed to MCI (due to AD or other causes) and dementia due to AD after the diagnosis has been confirmed by the Progression Adjudication Committee.

Section 12: Updated references

Section 13.4: Added table for reference

Amendment 4.01DE (Apr 2018)

This amendment is specific to Germany and includes changes required by BfArM and PEI (dated 14 February 2018):

- Clarification that Germany will not be participating in the tau PET substudy and will use the locally licensed amyloid ligand, florbetaben.

These changes will be incorporated in the next global amended protocol version 05 together with these DE specific changes.

Amendment 4 (Nov 2017)

This amendment includes:

- Alignment with recent CNP520 IB update (Edition 4 released 25-Aug-2017) reflecting new data from:
  a. GLP embryo-fetal development studies: CNP520 is not genotoxic nor teratogenic, therefore, male contraception is no longer required
  b. A pooled concentration-effect analysis of Holter- and 12-lead-ECG QT data from Phase 1 and Phase 2a studies: results did not indicate any relevant QT prolongation by CNP520, therefore current cardiac monitoring is adequate.
- Inclusion of tau PET assessments to assess neurofibrillary tangle burden as a secondary endpoint (voluntary, only at sites that can access tau tracer and have the required imaging capability)
- A randomization halt to Cohort I is introduced to mitigate the risk that a large number of participants are exposed to CAD106 prior to the futility analysis on CNS activity. Recent data with immunotherapies indicate that a robust effect on CNS activity should be sought to maximize chances that a clinical benefit might emerge following longer treatment. Re-commencement of randomization will be determined based on the evaluation of the futility analysis results by DMC.
- New Section 7.5: Reporting of study treatment errors including misuse/abuse
- Additionally, minor administrative changes and clarifying content changes are included, such as further details regarding study team roles, role of DMAG for follow-up of non-HMs, alignment with Study CCNP520A2202J, etc.

Amendment 3 (Jun 2017)

This amendment includes:

- 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 ^{18}F-florbetapir (e.g. ^{18}F-flutemetamol and ^{18}F-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 is fully recruited in order to enable a concurrent read-out of Cohort II and the parallel study with CNP520 (CCNP520A2202J – Generation Study 2).
- Additionally, feedback from investigators, other health authorities and ethics committees in other countries and updates for consistency with Study CCNP520A2202J are incorporated in this global amended protocol version 03.

Amendment 2.01DE (Apr 2017)

The current amendment to protocol version 02 addresses the changes required by BfArM and PEI dated 17 February 2017. No other changes are included.

Feedback from investigators, other health authorities and ethics committees in other countries have been received in parallel, and will be incorporated in the next global amended protocol version 03 together with these Germany specific changes.

Amendment 2.01UK (Mar 2017)

The amendment to protocol version 02 addresses the changes required by MHRA in their Non-Acceptance letter dated 24Feb2017. No other changes are included. Regulatory Authorities in countries where this clinical trial is being performed will be informed of this amended v02.01UK as applicable per local requirements.

These changes will be incorporated in the next global amended protocol version 03 together with these UK specific changes.

Amendment 2 (Sep 2016)

This amendment addressed the activation of Cohort II (CNP520 and matching placebo). The amendment also includes some clarifications of the protocol following feedback from investigators, health authorities and ethics committees on the previous version.

Amendment 1 (Oct 2015)

This amendment addressed the Special Protocol Assessment comments received from the US Food and Drug Administration (FDA) on 18-Sep-2015.

Protocol summary

Protocol number	CAPI015A2201J
Title	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 (AD).
Brief title	Study of efficacy of CAD106 and CNP520 in comparison to respective placebo in participants at risk for the onset of clinical symptoms of Alzheimer's disease.
Sponsor and Clinical Phase	Novartis Clinical phase II / III
Investigation type	Cohort I: Vaccine/Immunotherapy, Cohort II: Drug. Allocation ratio 1:4 between Cohort I and Cohort II until approximately 65 participants have been randomized to Cohort I. Subsequently, allocation ratio will change to 0:5 between Cohort I and Cohort II. Potential to resume recruitment for Cohort I is dependent on the results of the futility analysis for Cohort I.
Study type	Interventional.
Purpose and rationale	The purpose of this study is to determine the effects of each of the two therapies given separately, each targeting amyloid, on cognition, global clinical status, and underlying pathology in participants at risk for the onset of clinical symptoms of AD. Cognitively unimpaired individuals with APOE4 homozygote (HM) genotype and age 60 to 75 years inclusive, at screening, are selected as they represent a population at particularly high risk of progression to Mild Cognitive Impairment (MCI) due to AD and/or dementia due to AD.
Primary Objective(s)	• To demonstrate the effects of CAD106 and CNP520, vs. respective placebo on Time-to-event (TTE), with event defined as a diagnosis of Mild Cognitive Impairment (MCI) due to AD or dementia due to AD, whichever occurs first during the course of the study. • 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 API Preclinical Composite Cognitive (APCC) Battery test score.
Secondary Objectives	Key secondary objective • To demonstrate the effects of CAD106 and CNP520 vs. respective placebo on global clinical status as measured by the change from Baseline to Month 60 in Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score. Secondary objectives • To demonstrate the safety and tolerability of CAD106 and CNP520, vs. respective placebo as measured by adverse events (AEs), and changes in the brain structural MRI, laboratory tests, non-cognitive neurological and psychiatric findings including self-reported Columbia Suicide Severity Rating Scale (eC-SSRS), vital signs and electrocardiogram (ECG). [redacted]

	• To demonstrate the effects of CAD106 and CNP520, vs. respective placebo on cognition as measured by changes from Baseline to Month 60 on the Total Scale score and individual neurocognitive domain index scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). • To demonstrate the effects of CAD106 and CNP520, vs. respective placebo on function as measured by the change from Baseline to Month 60 in the Everyday Cognition scale (ECog) total scores reported by the participant and study partner, respectively. • To demonstrate the effects of CAD106 and CNP520, vs. respective placebo on AD-related biomarkers (amyloid deposition and measures of neurodegeneration) as measured by change from Baseline to Months 24 and 60 in the subset of participants who consent, on: o Binding of amyloid tracer and Tau tracer obtained using brain positron emission tomography (PET) imaging, o Volumetric MRI measurements, and o CSF/blood $A\beta_{40}$, $A\beta_{42}$, total tau and phospho-tau_{181} levels and NFL. <u>Specific objectives for Cohort I (CAD106 or placebo)</u> • To demonstrate the effects of antibody response to CAD106 vs. placebo on cognition as measured by the change from Month 6 to Month 60 in the APCC test score. • To describe amyloid-beta (Aβ)-specific antibody titers and serological responder rates over 60 months as measured by peak concentration and area under the concentration curve (AUC) of antibody titers and throughout the study. <u>Specific objectives for Cohort II (CNP520 or placebo)</u> • To demonstrate the effects of CNP520 vs. placebo on cerebral amyloid angiopathy (CAA) as measured by micro-hemorrhages and white matter hyper-intensities on MRI
Study design	This study protocol has multiple epochs with two informed consents required: • Pre-screening Epoch and Genetic Disclosure Follow-up (Informed consent #1) – also includes an optional genotyping only step (#1A); • Screening, Treatment and Follow-up Epochs (Informed consent #2). The Pre-screening Epoch includes assessments for evaluation of disclosure of APOE genotype to participants; 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 one investigational treatment or its matching placebo. Participants will be treated for at least 60 months up to a maximum of 96 months, and no longer than when the target number of events for the TTE endpoint has been observed and confirmed in the respective cohort. Individual participant treatment duration will depend on the timing of randomization in the course of the study, i.e. initially recruited participants will be treated at least until the last participant in the corresponding cohort reaches approximately 60 months of treatment.
Population	The Treatment Epoch population will consist of male and female participants at risk for the onset of clinical symptoms of AD, based on their APOE4 HM genotype and age (60 to 75 years of age, inclusive, at the time of screening).

	Approximately 1340 participants will be randomized in approximately 145 centers worldwide across the two cohorts (target of N = 690 in Cohort I (recruitment halt after approximately 65 participants are randomized) and N= 650 in Cohort II) with an allocation ratio of 1:4 for Cohort I to Cohort II until completion of recruitment in Cohort II. An unbalanced randomization (active: placebo) of 5:3 ratio in Cohort I (430 CAD106:260 placebo) and 3:2 ratio in Cohort II (390 CNP520:260 placebo) will be applied. Randomization will be stratified by age group (60-64 years, 65-75 years) and region (North America/Other, Europe).
Inclusion criteria	**Pre-screening Epoch and Genetic Disclosure Follow-up inclusion criteria** 1a. Written informed consent (Informed consent #1) obtained before any assessment is performed, including consent to receive disclosure of their APOE genotype. 2a. Male or female, age 60 to 75 years inclusive, at the time of signing Informed consent #1(same age restriction also applied at Informed consent #2). • Once the cap of approximately 20% of total participants in the age group 60-64 years (at the time of signature of ICF#2) is met, a restriction to this age group will apply. Note: the same age limitations of 60-75 years, inclusive is also applied at the time of signing Informed consent #2 3a. 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. 4a. Mini-Mental State Examination (MMSE) total score ≥ 24 (can be based on documented result obtained in previous 3 months). 5a. Psychological readiness to receive APOE genotype information based on pre-disclosure rating scales, specifically: 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. 6a. Participant is 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). 7a. Participant's willingness to have a study partner for the Screening and Treatment epoch. **Screening and Treatment Epoch inclusion criteria** Participants eligible for inclusion must fulfill all of the following criteria prior to randomization:

	1b. 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 Informed consent #2; after reaching the maximum of 20% in the younger age group of 60-64 years, only those 65-75 years will be eligible.) 2b. 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, including continued psychological readiness for participating in the study as determined by clinical judgment. 3b. Homozygous APOE4 genotype. 4b. Cognitively unimpaired as defined by At the screening visit, score of 85 or greater on the RBANS delayed memory index score AND Clinical Dementia Rating (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. 5b. 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. 6b. Study partner, who spends sufficient time with the participant, and agrees to participate in the study must have adequate functioning (e.g. intellectual, visual, and auditory) and be fluent in, and able to read, the language in which study assessments are administered. • Accompany the participant to all required twice yearly visits • Meet the definition of a “study partner” as described in Appendix 4
Exclusion criteria	**Pre-screening Epoch and Genetic Disclosure Follow-up exclusion criteria** 1a. Any disability that may prevent the participant from completing all study requirements (e.g., blindness or deafness that is not appropriate for age, severe language difficulty, etc.).

	2a. Current medical or neurological condition that might impact cognition or performance on cognitive assessments e.g., MCI, dementia, Huntington's disease, Parkinson's disease, Lyme disease, syphilis, schizophrenia, bipolar disorder, active major depression, attention-deficit / hyperactivity disorder (ADD / ADHD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), active seizure disorder, history of traumatic brain injury with loss of consciousness and ongoing residual transient or permanent neurological signs/symptoms including cognitive deficits, and/or associated with skull fracture, alcohol/drug abuse or dependence currently, or dependence within the last two years. 3a. 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 or Human Immunodeficiency Virus (HIV) infection (based on a positive lab result for HBV/HCV and/or HIV, to be performed during screening if not available from the last 12 months), severe renal impairment, severe hepatic impairment, uncontrolled or significant cardiac disease including recent (within six months) myocardial infarction, congestive heart failure (New York Heart Association [NYHA] functional class III-IV), unstable angina, or long QT syndrome. 4a. 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. 5a. History of hypersensitivity to any of the investigational drugs or their excipients/adjuvant, or to drugs of similar chemical classes. 6a. Indication for or current treatment with Cholinesterase Inhibitors (ChEIs) and/or another AD treatment (e.g. memantine). 7a. Contraindication or intolerance to MRI or PET investigations (with fluorinated radioligands). **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: 1b. 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 (score of 3 on the Wahlund's scale in 2 or more bilateral brain regions), recent stroke, recent cerebrovascular disease evidenced by more than one lacunar infarct ≤ 20 mm or any single infarct > 20 mm, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformation, subdural hematoma or space-occupying lesions). For Cohort I (CAD106) only, in addition, evidence of Amyloid Related Imaging Abnormality-hemorrhages (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 central nervous system (CNS) or evidence of a prior cerebral macrohemorrhage (> 10 mm diameter) 2b. Score “yes” on item four or item five of the Suicidal Ideation Section of the eC-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 is included in the Suicidal Behavior Section) if this behavior occurred in the past two years prior to screening. 3b. A positive drug screen at Screening, if, in the Investigator’s opinion, this is due to drug abuse or dependence. Participants with a positive drug screen not believed to be related to drug abuse or dependence (e.g. presence of prescription drugs in urine without evidence of prescription drug abuse), can be re-screened once. 4b. Significantly abnormal laboratory results at Screening as described in Appendix 1.4 or meeting the exclusionary alert values as 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. 5b. Clinically significant “active” infection which has not resolved within two weeks prior to initial dosing. In that particular case, delayed randomization may be considered. 6b. Current significant ECG findings as reported by central reader that are assessed as clinically significant by the investigator (e.g. sustained ventricular tachycardia, significant second or third degree atrioventricular block without a pacemaker, long QT syndrome or clinically meaningful prolonged QT interval). QTc interval > 500ms is exclusionary. 7b. Use of other investigational drugs prior to screening until: • Blood concentration has returned to Baseline or below Serological responder threshold for 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., Beta-site-APP Cleaving Enzyme - 1 (BACE-1) inhibitors. 8b. 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 (examples include, but are not limited to, clozapine, cancer medical treatments like tamoxifen, systemic immunosuppressive drugs like methotrexate and interferon, or other immunosuppressive biological medicines for rheumatic diseases or multiple sclerosis). • In the four weeks prior to randomization and/or current treatment with any CNS active drug(s) with exceptions described in Table 5-3. • For Cohort I (CAD106) only: Treatment with warfarin or other coumarin derivatives, or with a combination of acetylsalicylic acid and an anti-platelet agent (e.g. clopidogrel) within seven days (or five half-lives, whichever is longer) prior to randomization, or current indication for chronic treatment with a direct anti-coagulant • For Cohort II (CNP520) only: Current chronic treatment (>3 months) with (see Table 5-2)

	• strong cytochrome P450 3A4 (CYP3A4) inducers or strong CYP3A4 inhibitors; • or drugs with a narrow therapeutic index known to be primarily metabolized by CYP2C or 3A isoenzymes, and sensitive Pgp substrates 9b. Violations of concomitant medication restrictions as described in Table 5-3. 10b. Donation or loss of 400 mL or more of blood within 8 weeks prior to screening lab tests or lumbar puncture, if applicable. 11b. 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. 12b. For Cohort II (CNP520) only: Participants with clinically relevant depigmenting or hypopigmenting conditions (e.g. albinism, vitiligo) or active / history of chronic urticaria in the past year. 13b. For Cohort I (CAD106) only: Participants with previous organ transplantation or stem cell transplantation Exclusion criteria for participation in lumbar puncture: 14b. 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 spinal conditions that in the judgment of the Investigator would preclude a lumbar puncture. **No additional exclusions may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible participants.**
Investigational and reference therapy	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. Participants will be given intramuscular (i.m.) injections at Weeks 1, 7, 13 and quarterly i.m. injections (every 13 weeks) thereafter, until the last injection 3 months prior to completion of the Treatment Epoch. Cohort II (CNP520 and placebo): Arm #3: CNP520 50 mg capsule for once daily administration (p.o.) administration; or CNP520 LDR Arm #4: Placebo to CNP520 50 mg capsule for one daily (p.o.) administration; or placebo to CNP520 LDR Participants will be dispensed medication supplies for 3-month treatment with CNP520 or matching placebo for oral intake for the duration of the Treatment Epoch.
Efficacy assessments	• MCI due to AD or dementia due to AD (MCI/dementia) (diagnostic verification form)

	• API Preclinical Composite Cognitive (APCC) Battery • Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) • Raven's Progressive Matrices • Mini Mental State Examination (MMSE) • Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) • Everyday Cognition Scale (ECog) • [redacted] • [redacted] • [redacted] • [redacted]
Safety assessments	• Physical and Neurological examination ([redacted]) • Vital signs • Height and weight • Laboratory evaluations • Electrocardiogram (ECG) • Safety brain MRI scans • Adverse events and serious adverse events • Columbia-Suicide Severity Rating Scale (eC-SSRS)
Other assessments	• Immune response (applicable to Cohort I [CAD106 or matching placebo] only) o A-beta specific antibody titers o A-beta specific IgG subtypes o A-beta and Q-beta specific T-cell lymphocyte response • [redacted] • Biomarkers o Imaging biomarkers • Volumetric MRI • [redacted] • Amyloid PET* • [redacted] • Tau PET* where locally permitted (i.e. not in Germany) o Fluid biomarkers • CSF-based biomarkers*

	• Blood-based biomarkers* (serum, plasma, [redacted] * Voluntary consent
Data analysis	The primary analysis comprises statistical tests of hypotheses on both primary endpoints. The statistical tests will compare each active investigational treatment versus matching placebo as control group. A pre-defined testing strategy will be used to adjust the type I error rate for testing more than one hypothesis. For both investigational drugs, primary analyses will be performed on both, the TTE endpoint and the APCC score. The following null hypotheses will be tested: • H_{01}: The active treatment arm does not differ from matching placebo with regard to the distribution of time to first diagnosis of MCI or dementia due to AD; • H_{02}: The active treatment arm does not differ from matching placebo in the mean change from Baseline to Month 60 in the APCC test score. The first hypothesis will be tested using a Cox Proportional Hazards Regression Model with treatment group as the factor of interest and adjusting for important baseline covariates (baseline APCC score, baseline amyloid load, region and age). The second hypothesis will be tested using a Mixed-effects Model for Repeated Measurements (MMRM) for the change from baseline with treatment group as the factor of interest, visit number to model the time course, and adjusting for important covariates (baseline APCC score, baseline amyloid load, region, age). Next to these primary analyses, sensitivity and supportive analyses are planned. For the TTE endpoint such analyses include stratified log-rank test and a Cox model with different missing values handling. For APCC, an MMRM model for the change score with a larger range of covariates, interactions terms and an MMRM model with different missing values handling will be performed. For the CAD106 cohort, analyses of primary endpoints will be repeated on an analysis set excluding serological non-responders. Secondary endpoints (CDR-SOB, ECog, individual scales included in the APCC battery and RBANS, amyloid, tau [redacted] PET, Volumetric MRI, NFL in blood/CSF, total tau, phosphorylated tau in CSF) will all be analyzed using longitudinal models, such as MMRM similar to the approach for the primary endpoint APCC, with treatment as main factor while adjusting for important covariates. For the secondary safety parameters (AEs, SAEs, laboratory results, vital signs, ECG, eC-SSRS, safety brain MRI scans) and for Aβ-IgG response to CAD106, descriptive statistics will be provided.
Key words	Randomization, Placebo controlled, Parallel – group, APOE4 Homozygotes, preclinical Alzheimer's Disease (AD) and Aβ lowering

1 Introduction

1.1 Background

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.

Investigational treatments targeting the AD pathogenic cascade include those intended to interfere with the production, accumulation, or toxic sequelae of amyloid-beta (Aβ) species (Kramp and Herrling, 2011). Strategies that target decreasing Aβ by: (1) enhancing the amyloid clearance with an active or passive immunotherapy against Aβ; (2) decreasing production through inhibition of Beta-site-APP cleaving enzyme-1 (BACE-1, an enzyme involved in the processing of the amyloid precursor protein [APP]), are of potential therapeutic value.

Based on animal data and limited benefits in recent clinical trials targeting dementia stages of the disease, there is a growing belief that the Aβ-lowering therapies might be most effective in preventing or slowing the progression of AD in the preclinical stages. This approach allows participants to be treated before, or in the very earliest stages of, symptoms and disease onset, prior to plateau of fibrillary Aβ, extensive appearance of tau (neurofibrillary) pathology and irreversible synaptic or neuronal loss.

In this context, and under the umbrella of the Alzheimer's Prevention Initiative (API) (API: a public-private partnership) intended to help the field accelerate the evaluation of investigational prevention therapies (Reiman et al 2011), this study, CAPI015A2201J (also referred to as Generation Study 1), will provide an opportunity to evaluate the effects of two amyloid targeted therapies (CAD106 and CNP520) in cognitively normal people who, on the basis of their age and genetic background (apolipoprotein E ε4 allele homozygotes [APOE4 HMs]), are at the highest imminent risk of developing symptoms of AD.

In this clinical trial, the identification of APOE4 HMs is employed as a prognostic enrichment strategy to select individuals with a greater likelihood of having substantial worsening in cognition, in a reasonable timeframe, that can be practically assessed within the setting of a clinical trial. APOE4 HMs are estimated to represent about 2 to 3% of the general population and are at much higher risk of developing symptoms of late–onset AD (LOAD) than people with other APOE genotypes, with a mean age of 68 years at onset (Corder et al 1993). Previously published estimates of lifetime risk of developing dementia due to AD by age 85 were 51 to 68% and 23 to 35% for APOE4 HMs and heterozygotes (HTs), respectively (Genin et al 2011). Risk estimates communicated in the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study, based on cross-sectional or case-control data, are 51 to 68% in APOE4 HMs and 22 to 52% in APOE4 HTs, (the risk of developing MCI due to AD was not separately estimated.). In preparation for this study, standardized risk information for the target population based on APOE4 genotype was compiled by independent researchers (Qian et al 2017). Risk estimates for developing MCI or dementia due to AD by age 85 were determined for each APOE genotype using data from four prospective cohort studies. The resulting estimate for the Generation Study 1 participants (60 to 75 years old) of the corresponding risk by 85 is

30 to 55% for HMs (E4/E4). This risk estimates will be used during the genetic disclosure session (Qian et al 2017).

It is proposed that APOE4 HM status enhances the risk for AD by affecting Aβ clearance, aggregation, and deposition (Liu et al 2013).

Based on current knowledge, the results might be generalized and applicable to preclinical AD beyond APOE4 HMs, since amyloid-targeted therapies are expected to reduce and/or prevent amyloid plaque accumulation, independent of the multiple potential causes of amyloid deposition in late-onset AD.

Trial outcomes and designs need to be established for pre-symptomatic stages of AD. Traditional measures of cognitive changes developed for studies in mild cognitive impairment (MCI) or dementia due to AD are of limited value due to the psychometric properties of the tests (e.g. ceiling effects). This study will employ two primary outcomes: time to diagnosis of MCI due to AD and/or dementia due to AD, and the API preclinical composite cognitive (APCC) test battery. The APCC battery was developed as a sensitive tool to detect and track cognitive decline in individuals at risk to progress to the clinical stages of LOAD (Langbaum et al 2014).

Although data are available for AD biomarkers in longitudinal cohorts, understanding of the extent to which treatment biomarker effects could predict clinical benefit is limited. By assessing different biomarkers of AD pathology, this study aims to address this question.

Lastly, the psychological and behavioral impact of disclosure of APOE genotype has been studied only in restricted settings (Green et al 2009, Roberts et al 2011). This study will improve our understanding of the impact of disclosing APOE4 HM genotype status and associated risk information to older adults, who are at more imminent risk of AD. Furthermore, by incorporating innovative models for delivery of genetic services for risk disclosure, the study will provide data on these delivery modalities for genetic education and counseling and will be essential in expanding the reach of and access to genetic counseling services, given the limited number of trained providers in this discipline (Patrick-Miller et al 2014).

CAD106

CAD106 is a second-generation active Aβ immunotherapy which comprises multiple copies of the $A\beta_{1–6}$ peptide coupled to a carrier containing 180 copies of bacteriophage Qβ coat protein.

CAD106 effectively induced Aβ antibodies in animal models, without activating an Aβ-specific T-cell response. Aβ antibodies were shown to reduce amyloid accumulation by enhancing amyloid clearance in multiple transgenic mouse models, with a stronger effect when administered in the early stages. Chronic toxicology studies in rabbits, transgenic mice, and Cynomolgus monkeys, using adjuvanted (aluminum hydroxide or MF59) and non-adjuvanted CAD106, supported progressing to trials in humans.

Clinical data generated so far includes a total of four double-blind, placebo-controlled clinical studies in Alzheimer patients and two open-label extension studies. Across all studies in 206 predominantly mild AD patients, CAD106 showed a favorable safety and tolerability profile. CAD106 was not associated with meningoencephalitis, symptomatic amyloid-related imaging abnormalities (ARIA) or other magnetic resonance imaging (MRI) findings, or adverse immune reactions. Exploratory results of central nervous system (CNS) biomarker data, following continuous exposure over 18 months to CAD106-induced antibody titers, were largely consistent with the expected effects of an Aβ-immunotherapy.

Further details on CAD106 are provided in the CAD106 Investigator's Brochure (IB).

CAD106 will be studied in Cohort I of the study API015A2201J, which will start when the first participant is randomized in the study.

CNP520

CNP520 is an orally active BACE-1 inhibitor with an approximately 3-fold selectivity for BACE-1 over BACE-2 and no relevant off-target binding or activity.

In animals, CNP520 reduces Aβ concentrations in cerebrospinal fluid (CSF) and the brain by up to 90%, following single and chronic administration. CNP520 has been investigated in fertility and early embryonal development study in rats, safety pharmacology and repeat-dose toxicity studies of up to 26 weeks duration in rats and 39 weeks in dogs by oral gavage. The results of these studies have not raised major safety concerns for clinical use.

CNP520 appeared generally safe and well-tolerated in four Phase I studies and one Phase IIa study with up to 3-month exposure duration conducted in healthy adults ≥60 years of age. Clinical data generated so far includes a total of 422 subjects who have been administered with CNP520 (n=335) or with matching placebo (n=87). Approximately two thirds (n=213) of the subjects were ≥60 years of age, thereby reflecting the age group of the proposed study population. A total of 100 subjects ≥60 years of age have received CNP520 for 3 months. Approximately 30% of participants were carriers of at least one APOEε4 allele.

In healthy subjects ≥ 60 years of age, CNP520 reduced CSF Aβ concentrations in a dose-dependent manner by up to approximately 80% at the maximum single dose tested (750 mg) and 95% after multiple dosing at the highest dose tested (300 mg q.d.). Aβ40 concentrations in CSF decreased by 91% compared to baseline after 3-month exposure at CNP520 85 mg q.d.

CNP520 undergoes predominantly oxidative metabolism via CYP3A4/5. Following 3 months of multiple dose administration of up to 85 mg CNP520 once daily, the mean terminal elimination half-life was approximately 150 hours. CNP520 showed good brain penetration, indicated by cerebrospinal fluid (CSF) concentrations similar to the unbound plasma concentrations following both single and multiple dose administrations.

Further details on CNP520 are provided in the CNP520 IB.

In October 2018, results of completed clinical trials evaluating other BACE inhibitors were made public:

- A Phase II study with elenbecestat showed a trend towards a positive effect on CDR-SB over placebo (p=0.55) in patients with MCI or mild to moderate AD (Lynch et al 2018).

- LY3202626 did not indicate a decline in cognitive performance over the duration of the trials (Lo et al, 2018).
- Two other compounds (verubecestat and atabecestat) were found to be associated with a decline in performance on tests of memory and other aspects of thinking starting in the first three to six months of treatment, along with more neuropsychiatric symptoms. The declines in cognitive performance were reported as mild and generally not detected at the individual level. (Egan et al 2018; Romano et al 2018)

Although CNP520 and the drugs being tested by other pharmaceutical companies all belong to the same class of drugs (BACE inhibitors), each drug has unique safety profile. Encouraging results obtained with a dose of LY3202626 that results in a 57% of CSF Aβ lowering indicates that benefit may still be expected at a medium level of BACE inhibition. (Lynch et al 2018). It is unknown whether the negative effects observed are due to BACE inhibition *per se* or due to other properties of the drugs. Thus it is unknown whether similar effects will be observed also for CNP520.

1.2 Purpose

The purpose of this study is to determine the effects of each of the two therapies given separately, each targeting amyloid, on cognition, global clinical status, and underlying pathology in participants at risk for the onset of clinical symptoms of AD. Cognitively unimpaired individuals with APOE4 HM genotype and age 60 to 75 years, inclusive, are selected as they represent a population at particularly high risk of progression to MCI due to AD and/or dementia due to AD.

2 Study objectives

2.1 Primary objectives

- 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 occurs first during the course of the study,
- 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 score.

2.2 Secondary objectives

Key secondary objective

- To assess the effects of CAD106 and CNP520, vs. respective placebo on global clinical status as measured by the change from Baseline to Month 60 in Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score.

Secondary objectives

- To assess the safety and tolerability of CAD106 and CNP520, vs. respective placebo as measured by adverse events (AEs), and changes in the brain structural MRI, laboratory tests, non-cognitive neurological and psychiatric examinations including the self-reported Columbia Suicide Severity Rating Scale (eC-SSRS), vital signs and electrocardiogram (ECG).
  - [redacted]
  - [redacted]
- To assess the effects of CAD106 and CNP520, vs. respective placebo on cognition as measured by changes from Baseline to Month 60 on the Total Scale score and individual neurocognitive domain index scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).
- To assess the effects of CAD106 and CNP520, vs. respective placebo on function as measured by the change from Baseline to Month 60 in the Everyday Cognition scale (ECog) total scores reported by the participant and study partner, respectively.
- To assess the effects of CAD106 and CNP520, vs. respective placebo on AD-related biomarkers (amyloid deposition and measures of neurodegeneration) as measured by change from Baseline to Months 24 and 60 in the subset of participants who consent on:
  - amyloid tracer and tau tracer (at the subset of sites with access to tracer and the required imaging capability) obtained using brain positron emission tomography (PET) imaging
  - volumetric MRI measurements, and
  - CSF/blood $A\beta_{40}$, $A\beta_{42}$, total tau and phosphorylated tau_{181} and NFL levels.

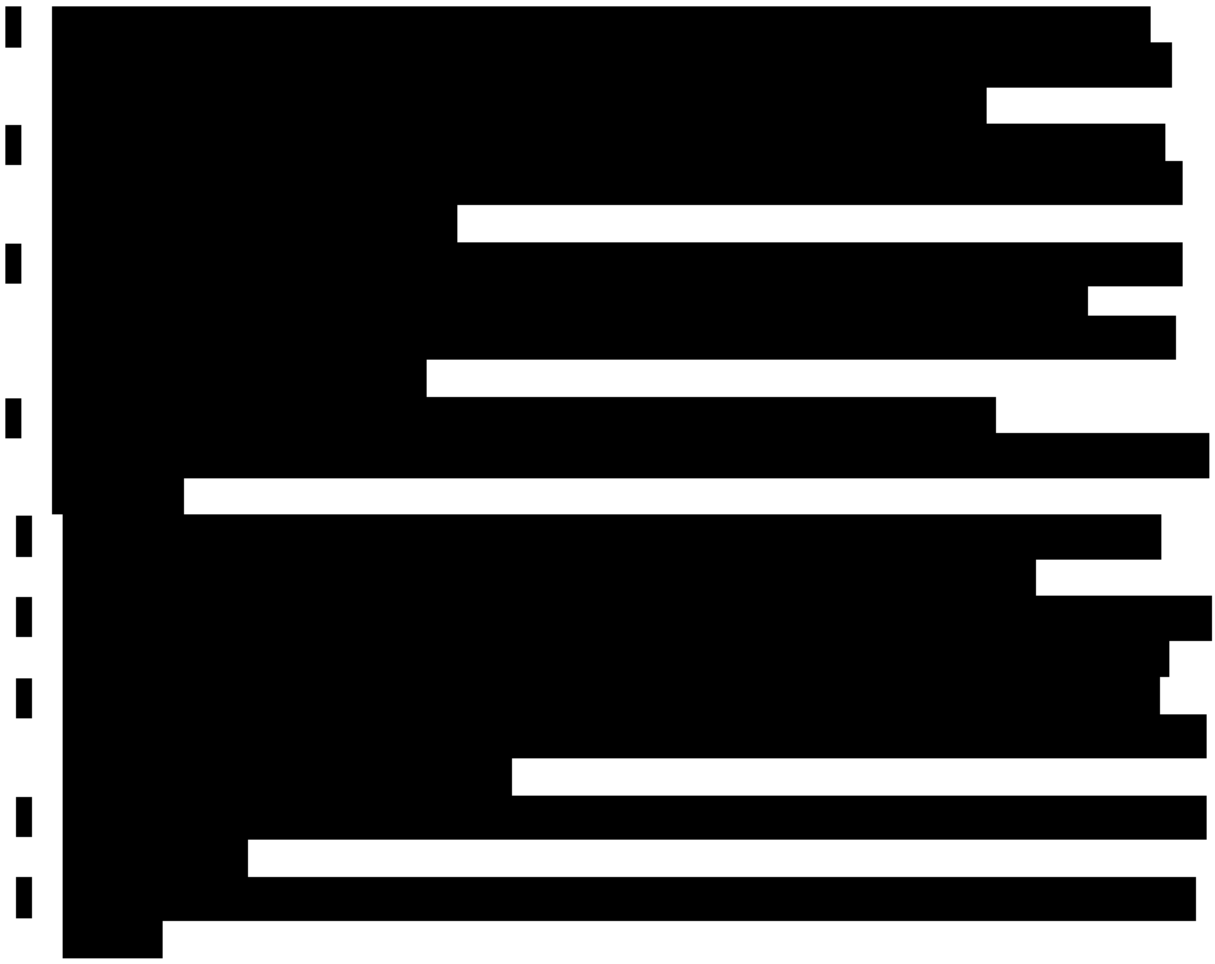
Specific objectives for Cohort I (CAD106 or placebo):

- To assess the effects of antibody response to CAD106 vs. placebo on cognition as measured by the change from Month 6 to Month 60 in the APCC test score and CDR-SOB.
- To describe Aβ-specific antibody titers and serological responder rates over 60 months as measured by peak concentration and area under the concentration curve (AUC) of antibody titers.

Specific objectives for Cohort II (CNP520 or placebo):

- To assess the effects of CNP520 vs. placebo on cerebral amyloid angiopathy (CAA) as measured by micro-hemorrhages and white matter hyper-intensities on MRI.

[redacted]



3 Investigational plan

3.1 Study design

This study protocol has multiple epochs with two informed consents required:

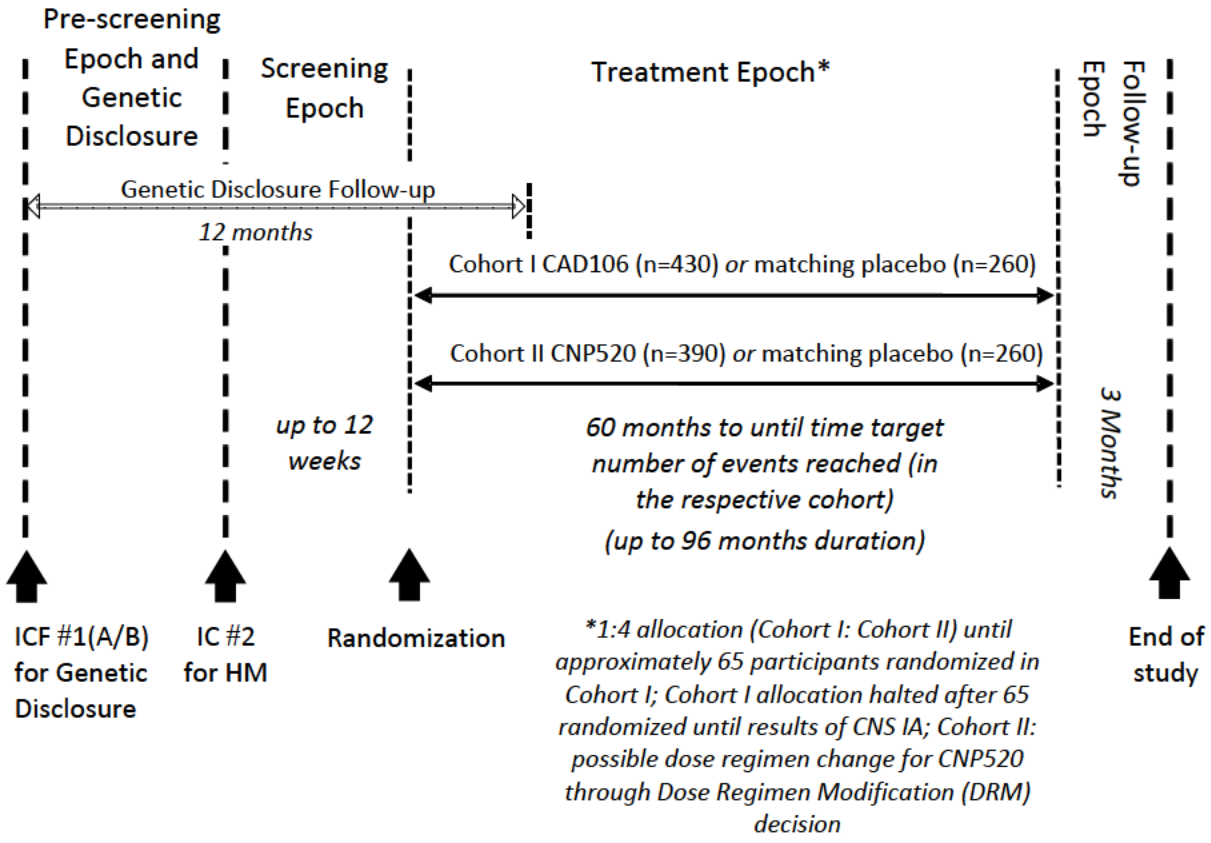
1. Pre-screening Epoch and Genetic Disclosure Follow-up (Informed consent #1)
2. Screening, Treatment and Follow-up Epochs (Informed consent #2).

The Treatment Epoch follows a randomized, double-blind, placebo-controlled, two-cohort parallel group design in which participants receive the one investigational treatment or its matching placebo (Figure 3-1).

The end of the Treatment Epoch for each cohort will be achieved when (1) all ongoing participants for the respective cohort have completed their month 60 assessment and (2) the target number of 218 events has been reached in the respective cohort (see Section 3.3), whichever is later. Participants will be treated for at least 60 months up to a maximum of 96 months, and no longer than until the target number of events for the TTE endpoint has been observed and confirmed in the respective cohort. Individual participant treatment duration will depend on the timing of randomization in the course of the study, i.e. initially recruited participants will be treated at least until the last participant reaches approximately 60 months of treatment.

In practice, the number of events will be monitored regularly in a blinded fashion within each cohort throughout the Treatment Epoch to estimate the time point when the required events (see Section 5.5.12 and Section 9.8) will occur. In case the expected number of events is significantly below expectation, then a change of treatment duration or other revisions of the study design might be introduced with a protocol amendment.

Figure 3-1 Study design



3.1.1 Pre-screening Epoch and Genetic Disclosure Follow-up

Informed consent #1 includes consent to receive disclosure of APOE genotype, description of all Pre-screening activities leading to genetic disclosure, the basic trial design and risks of investigational drugs for potential study participation of HMs, as well as the Genetic Disclosure Follow-up assessment telephone calls for all participants who received disclosure of their genotype.

The population participating in the Pre-screening Epoch and Genetic Disclosure Follow-up will consist of HMs and non-HMs in the age range of 60-75 years, inclusive, at the time of Screening (ICF#2). Age distribution will be controlled for HMs eligible to continue in Screening Epoch, with a maximum of about 20% of the participants are 60 - 64 years old, inclusive at Informed consent #2. Beyond this threshold, the population eligible will be limited to participants in the age range of 65-75 years.

Potential study participants will be invited for Pre-screening through a variety of sources and methods. Examples are presented in Appendix 2. Potential participants may be genotyped in an initial step with no commitment to be invited for the study. In such cases, the site will apply a ratio of HMs and non-HMs to avoid implicit disclosure by invitation.

Upon signature of Informed consent #1 (Figure 3-2), participants will be screened using a limited set of eligibility criteria (see Section 4.1). The fulfillment of these criteria does not automatically signify eligibility to enter the Screening, Treatment and Follow-up Epochs. It is recommended that study personnel performing the Pre-screening assessments prior to genetic disclosure be blinded to the genotype of the participant, unless the participant joins with prior knowledge of her/his genotype. If this is not possible, site personnel must take additional precautions to avoid inadvertent disclosure of APOE4 genotype to the participant prior to the formal disclosure session with the genetic counselor.

Following the completion of the Pre-screening assessments, a genetic counselor, or such equivalent according to local regulations (e.g. trained psychologist, study nurse or clinician), will speak with the study personnel who performed the Pre-screening assessments to share the assessment scores. For those referrals without prior genotype disclosure, the counselor will then assess the participant's psychological readiness to receive her/his APOE genotype based on the participant's Pre-screening assessment scores (including specific cut-offs described in Section 4.1) and the counselor's and investigator's clinical judgment. It is recommended that the genetic counselor is blind to the participant's APOE4 genotype prior to the counseling session (unless the genotype was already known to the participant), to ensure an unbiased counseling session.

After psychological readiness is confirmed by the Investigator, the counselor will proceed with the genetic counseling session and confirm with the participant during the counseling session that she/he is ready and willing to receive his/her genotype. Once confirmed, the counseling session will continue with genetic disclosure using Standardized APOE Risk Information across all sites, which will have been reviewed by the ECs/IRBs.

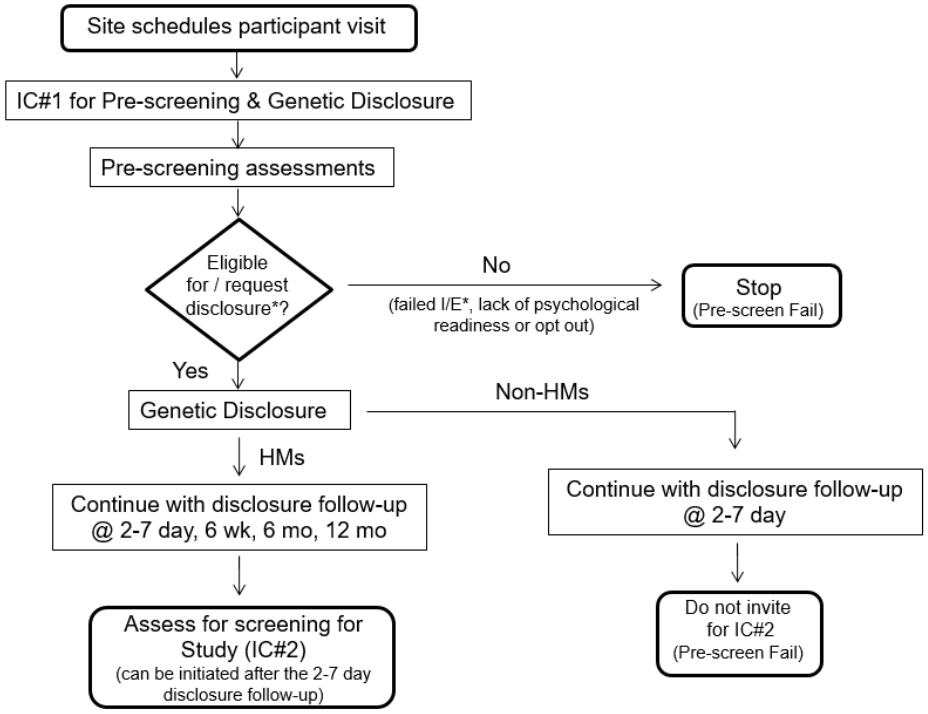
If a participant fails eligibility, he/she will be considered as "prescreening failure" prior to genetic counseling/disclosure. Genetic disclosure will the therefore not occur unless local regulations mandate the right to know genotyping results. If the participant still requests to learn his/her genotype, communication of the result may be considered on a participant by participant basis if deemed appropriate by the Investigator, as long as psychological readiness has been verified. Communication of the genotyping results in such cases will be organized by the Investigator in accordance with local regulations, including any follow-up requirements, outside of this clinical study.

All participants who were informed of their genotype will be assessed, via telephone questionnaires, for the impact of genetic disclosure. For HMs, these assessments will occur approximately 2 to 7 days, 6 weeks, 6 and 12 months later (see Schedule of Assessments, Table 6-1). For non-HMs, only the first (2 to 7 day) evaluation is required. All participants who declined to receive information about their genotype or were deemed not ready psychologically to receive it, will be considered as Pre-Screen failures.

At the 6-week genetic disclosure follow-up phone call, the site should follow up with any eligible HM that has not already signed ICF#2 to determine confirmation of the participant's interest to continue to the next part of the study. The population eligible for the Treatment Epoch does not include participants who carry only one APOE4 allele (HTs); these participants may have the option to enroll in the Novartis Study CCNP520A2202J. If the participant consents to this sister study, personal data and other information from that other study may be transferred to the database of study CCNP520A2202J.

An independent Disclosure Monitoring Advisory Group (DMAG) will monitor the genetic disclosure safety data. The DMAG is responsible for assisting the Data Monitoring Committee (DMC) in an advisory capacity. (Refer to Section 8.6)

Figure 3-2 Pre-screening Epoch and Genetic Disclosure Follow-up flow chart



*If a participant fails I/E, he/she will be registered as "prescreening failure" prior to genetic counseling/disclosure and therefore genetic disclosure will not occur. If the participant still requests to learn his/her genotype, communication of the result may be considered on a participant by participant basis, as long as psychological readiness has been verified. Communication of the genotyping results in such case will be organized by the investigator outside of this clinical study, unless local regulations mandate the right to know genotyping results.

IC = Informed consent; HM = homozygote E4; non-HM = heterozygotes or non-carriers; I/E = Inclusion and Exclusion criteria

3.1.2 Screening Epoch and Treatment Epoch

3.1.2.1 Screening Epoch - for APOE4 homozygotes only

The population participating in the Screening Epoch will consist of only APOE4 HMs. Age distribution will be controlled by ensuring that a maximum of about 20% of the participants randomized are <65 years, with the remaining 80% of the participants randomized in the 65 years and older age bracket. Eligible HMs will be invited to sign the Informed consent #2 after the impact of the genetic disclosure is assessed, at least 2 to 7 days later. Additionally, the investigator/mental health care provider (as per local regulation), will apply clinical judgment and invite only those participants who continue to show psychological readiness for participating in the study.

Informed consent #2 will be signed at the start of the Screening Epoch and will describe the detailed assessments for the entire trial. The Screening Epoch assessments will be performed over a maximum of 12 weeks duration from the timing of ICF#2 signature (see Section 4.2 and Section 6.2). This 12-week time frame may be extended in case of logistical issues (e.g. some assessments may have been unexpectedly rescheduled) only if the certain conditions are met. Refer to Section 6.3.5.

Participants who fail eligibility during the Screening process for a temporary condition (e.g. active infections, concomitant medications, etc.) should be screen failed, however will be allowed to be re-screened at a later stage, when all inclusion and exclusion criteria will have to be re-verified. At the Baseline visit, eligible participants will be randomized to one of the four treatment arms across the two cohorts (see Section 5.3).

3.1.2.2 Treatment Epoch - for APOE4 homozygotes only

The Treatment Epoch will consist of approximately 1340 participants to be randomized in approximately 145 centers worldwide across the two cohorts (target of N = 690 in Cohort I (recruitment halt after approximately 65 randomized, see Section 3.2) and N = 650 in Cohort II).

Only participants who are confirmed to be HMs and satisfy all of the Screening and Treatment Epoch eligibility criteria will be randomized to the double-blind Treatment Epoch. Participants will be randomly allocated to either Cohort I or Cohort II in a 1:4 ratio to favor recruitment to Cohort II (see Section 3.2 and Section 5.3 for rationale) until Cohort II is fully recruited. Once approximately 65 participants are randomized in Cohort I, allocation will be shifted to Cohort II only until results of the futility analysis are obtained). Recruitment in Cohort I may resume based on the results of the CNS activity futility analysis. (See rationale below in Section 3.2, and details of the CNS activity futility analysis in Section 9.6).

- If CAD106 meets the futility criteria no further participants will be randomized to Cohort I and the cohort will be closed. Previously treated participants in Cohort I will be discontinued from treatment and offered to be re-randomized in Cohort II (see Section 5.5.9).

If CAD106 does not meet the futility criteria and sufficient CNS activity is observed, randomization will re-commence until all planned participants to Cohort I are recruited (see Section 5.3).Within each cohort respectively, an unbalanced randomization (active: placebo) of 5:3 ratio in Cohort I (430 CAD106: 260 placebo) and 3:2 ratio in Cohort II (390 CNP520: 260 placebo) will be applied. Cohort I participants will receive intramuscular (i.m.) injections of CAD106 with Alum or placebo with Alum at the study site every 6 weeks for the first 3 injections and then every three months (approximately 13 weeks).

Cohort II participants will be dispensed medication supplies for 3-month treatment with CNP520 or matching placebo for oral intake.

From the Baseline visit on, participants will attend clinic visits every three months for dispensation of study medication and at 3 months and 6 months during the first year and then every six months to assess full safety and efficacy. In addition, Cohort I participants will also attend visits at Weeks 7, 9 and 15 specifically for antibody titer measurements. Following completion of the Treatment Epoch, participants will be asked to attend a Follow-up visit 3 months later, i.e. 6 months after last injection in Cohort I or within 3 months of mTEC visit for Cohort II.

Safety assessments, as detailed in Section 6.5, will include regular standard assessments (e.g. vital signs, electrocardiograms [ECGs], laboratory tests), as well as specific assessments related to potential CNS or other safety assessment requirements (e.g. skin assessment for CNP520), depending on the cohort. Brain MRI scans, for monitoring of cerebrovascular pathology and detection of ARIA, will be completed every 6 months during the first year, and on an annual basis subsequently in both cohorts. The scans will be read centrally at the Imaging Clinical Research Organization (CRO), with safety reports provided to the Investigators and Medical Monitor. Guidance to the Investigators in case of new findings is provided in Section 13.

Efficacy assessments, as detailed in Section 6.4, will be conducted every six months until the end of the study. Although the study partner is expected to come to the site with the participant to all relevant visits, if that proves impossible, his/her input can be obtained by telephone interview. At each visit, the Investigator will assess the participant for the presence of MCI or dementia using pre-specified criteria described in Section 6.4.1. In the event of a positive finding, the Investigator will submit a narrative description for assessment by the Progression Adjudication Committee (PAC), which will review the data according to a predefined charter (see Section 8.5).

An independent Data Monitoring Committee (DMC) will monitor the safety and efficacy data (see Section 8.4). Multiple interim analyses (IAs), supervised by the DMC (Section 3.5), are planned based on data collected for safety, immunogenicity for CAD106, CNS biomarkers and clinical endpoints, throughout the study. The main purpose of the planned IAs will be safety monitoring and futility, with the potential consequence of discontinuing the applicable cohort in scope for the IA. If, at the time of the primary endpoint IA, futility for the applicable investigational drug is not met, the sponsor will plan an open-label extension study with the respective treatment to be initiated after individual participants complete the double-blind phase of the study.

See Table 6-2, Table 6-3 and Table 6-4 for Screening Epoch, Treatment Epoch and Follow-up Epoch assessments.

3.1.2.3 Biomarkers

All eligible participants will be required to complete MRI and brain amyloid assessment with an amyloid PET scan (alternatively, a lumbar puncture to measure Aβ in the CSF could be used if amyloid PET scan is not available) prior to randomization. MRI evaluations at 6 – 12 months intervals will then be conducted in all participants. The second amyloid PET scan at 24 months will be conducted in all participants who had a baseline amyloid PET scan and must use the same amyloid locally approved PET ligand that was used at baseline (see Section 6.6.3.1). Individual results of the PET scans and any fluid biomarker assessments will not be disclosed to the Investigators or participants prior to study completion.

Participants will be encouraged to contribute to additional investigations of AD and relevant biomarkers, upon specific consent. These include optional consent to Tau PET scans (at the subset of sites with access to the tau tracer, where locally permitted, and the required imaging capability, at Screening, Month 24 and Month 60, an additional amyloid PET scan at 60 months, [redacted]), and CSF and blood-based soluble biomarkers at Baseline, Month 24 and Month 60 as described in Table 6-2 and Table 6-3. In locations where compliance with total radiation exposure limits could be of concern, voluntary Tau PET scans will be prioritized [redacted].

The participant will not have access to his/her individual results (e.g. fluid biomarkers, [redacted] or imaging results) as knowledge of the results (specifically in relation to amyloid or glucose metabolism) could inadvertently unblind the participant or investigator. Results of these tests will not be available until study completion. Any clinically significant safety findings that require follow up will be communicated to the participant and results of subsequent clinical scans will be shared in real-time.

All data, samples and images collected during the study, including the biomarker data, will be anonymized and stored in central repositories. After recruitment has been completed, baseline characteristics might be shared with the research community for publication purposes. After study completion, data, images and biological samples may be made available to the research community per local requirements and regulations.

The data sharing will be overseen by an independent oversight committee that will assess the scientific validity of the research proposals.

3.1.2.4 Extended SAE collection for Cohort I participants

After the end of study (Follow-up visit), Extended SAE collection will be implemented for 1 year after the last study visit or for 1 year after the last injection in case of premature withdrawal (see Section 6.2 and 7.2.2). This safety monitoring will consist of SAE collection to be conducted for **all** participants who received at least one injection of study medication. This will encompass up to four quarterly telephone calls to the participant and/or study partner for a maximum of 12 months. SAEs occurring during this 1 year extended monitoring will only be captured in the Novartis safety database and not in the clinical database/ electronic case Report Forms (eCRFs).

3.2 Rationale for study design

The design of this study addresses the primary objective, which is to assess independently the effects of two amyloid-targeting therapies vs. placebo in participants at risk for the onset of clinical symptoms of AD over at least 60 months.

Population

The identification of individuals within the target age group of 60-75 years with APOE4 HM genotype is employed as a prognostic enrichment strategy for selecting individuals with a greater likelihood of having substantial worsening in cognition in a reasonable time frame (FDA, draft AD Guidance for Industry, 2013). For AD in general, and also with the HM genotype, risk of progression to MCI due to AD or dementia due to AD increases with age (Genin et al 2013, Qian et al 2017, Janssen et al. 2016, Bonham et al 2016). To ensure that a sufficient proportion of participants progress towards diagnosis of MCI or dementia due to AD during the trial, the study will randomize no more than approximately 20% of participants in the lower age group (<65 years). Due to the stratified randomization, the randomization ratios will be reflected within the two defined age groups of <65 years and 65 years and older. Details are provided in Section 5.3).

Design Features

This study will evaluate two active treatments, CAD106 and CNP520, in separate cohorts, each with a matching placebo arm. In order to enable a concurrent read-out of Cohort II and the parallel study with CNP520 (CCNP520A2202J – Generation Study 2), a 1:4 ratio for Cohort I versus Cohort II has been implemented.

A halt in randomization to Cohort I is introduced when approximately 65 participants are randomized to mitigate the risk that a large number of participants are exposed to CAD106 prior to the futility analysis on CNS activity. Although the extent of reduction of amyloid PET and the associated clinical effect in AD prevention are not known yet, recent data with immunotherapies indicate that a robust effect on CNS activity should be sought to maximize chances that a clinical benefit might emerge following longer treatment (Sevigny et al, 2016). In a previous study in mild AD (refer to CAD106 IB), CAD106 (n=11) showed ~3% difference in amyloid PET after 18 months in serological responders (80% of subjects) to placebo+non-responders (n=4). Higher effects might be observed in the Study API015A2201J due to the longer exposure to antibodies and lower amyloid load in the earlier stage of the disease. The available data provided at 24 months from 65 randomized participants will provide sufficient evidence to assess the futility criteria based on current knowledge. Resuming the allocation to Cohort I will be determined by results of the futility analysis on CNS activity, as reviewed by the DMC.

To optimize acceptability of the study, a greater proportion of participants will be allocated to active treatment or drug over placebo within each cohort.

- Cohort I (CAD106 or placebo) will use a 5:3 randomization ratio, which also accounts for the 10% of participants who may demonstrate an insufficient serological response, based on the individual CAD106-induced Aβ-specific IgG titer values in serum. The Serological response criteria (see Section 9.5.5 for definition) were developed in the course of the

previous Phase II studies. Changes both in CNS biomarkers and peripheral plasma Aβ were observed in Serological responders (SR). In this study, participants who do not develop Aβ-specific IgG titers fulfilling the SR criteria will not be discontinued from treatment. This is deemed ethically and scientifically justified since potential benefit to these participants cannot be ruled out completely as the relationship of biomarker changes to clinical outcomes is unknown. The continued treatment along with other participants will allow reliable conclusions to be drawn with respect to both potential benefit in Non-responders (NR) and cut-off for SR. Furthermore, risks in NR who are receiving CAD106 are not deemed higher than in those receiving Placebo.

- Cohort II (CNP520 or placebo) will use a 3:2 randomization ratio.

The approach of testing two active treatments in one study was chosen since the main study design features (population, efficacy outcomes, and study duration) may be applied for both CAD106 and CNP520. It is thought that the benefits of the operational efficiencies of a single study and the opportunity to pool placebo outweigh the drawbacks associated with the complexity of the study design (see Section 9.4). Furthermore, providing two active treatments in a single study would provide additional options for this population: if one cohort is terminated, the participants may be eligible to be reassigned to the other cohort (See Section 5.5.9).

Dose regimen modification

For Cohort II, the initial regimen is a once daily dose of 50 mg CNP520 or matching placebo throughout the full treatment epoch. If it is determined that the current doses do not provide a suitable benefit/risk profile, a single Lower Dose Regimen (LDR) will be implemented for the active treatment arm through a Dose Regimen Modification (DRM) process (see Section 5.1.2 and Section 5.2). This process may be triggered based on DMC recommendation and/or other data from studies becoming available for CNP520 or other BACE inhibitors.

In case of DRM, the LDR will consist of a single lower dose regimen selected - either a 50 mg once weekly dose or a 6 mg once daily dose. Both dose regimens are expected to have a similar safety profile. The selection of the dose regimen will be based on both the timing of the DRM decision, as this may restrict options based on availability of supplies, and any further information available at that time, including PK/PD modeling, external data, etc.

In case of DRM, the objective of the study will be to compare effects of the overall long-term exposure to CNP520 through the whole study duration across the dose and regimen used versus placebo.

The decision to introduce the option for DRM was not driven by data of the clinical trial, but on other sponsor's BACE inhibitor results. In addition, the DRM will keep main design features unchanged including the statistical testing procedure.

Primary Endpoints

There are two primary endpoint variables: the Time-to-event (TTE), with event defined as diagnosis of MCI due to AD or dementia due to AD and the APCC test score. The success of the study for each investigational drug will be determined by a positive result in at least one endpoint.

The main primary endpoint is defined as time to diagnosis of MCI due to AD or dementia due to AD (whichever is diagnosed first). Postponing the diagnosis of MCI and/or dementia represents an important clinical outcome with high face validity. The diagnostic criteria proposed by the National Institute on Aging Alzheimer's Association working group will be used (Albert et al 2011, McKhann et al 2011), alongside a centralized adjudication process (further details see Section 6.4.5).

The alternative primary endpoint, APCC test score, will allow examination of drug effects using a continuous measure of cognition. The APCC test was developed based on data from multiple longitudinal observational cohorts in unimpaired individuals at baseline in the target age-range. This was empirically derived from a series of independent analyses in six cohort datasets. The APCC test score has the sensitivity to detect and track preclinical cognitive decline in individuals who subsequently progress to the clinical stages of LOAD. It provides a single measure of multiple cognitive domains (e.g. episodic memory, executive function, visuospatial function) capable of detecting and tracking cognitive decline in people at particularly high risk for developing symptoms due to AD. Although the APCC test is expected to have the greatest sensitivity to detect and track cognitive decline in preclinical AD (decline that is due to AD and not aging), it is acknowledged that the APCC test score's sensitivity to treatment effects is still unproven. Additional APCC data is planned to be collected outside the API015 study, so that its relevance can be established in validating the natural history of the disease as well as its value to predict functional decline.

Individual assessments selected for inclusion in the APCC test battery are described in Section 6.4.2.

Secondary Endpoints

CDR-SOB (global measure widely used in clinical research in AD), RBANS total score (clinical tool used to assess the neuropsychological status), and ECog (measurement of daily function and subjective/study partner memory concerns) will be included as secondary endpoints, in order to fully capture potential drug effects and to further contribute to the assessment of clinical relevance of the potential treatment effects (see further information in Section 6.4).

The study will also investigate the effects of CAD106 and CNP520 on the underlying AD pathology (amyloid pathology and neurodegeneration) assessed by biomarker data.

These AD biomarker data will be used to assess CNS activity (target engagement and downstream effects) for each investigational treatment in an unblinded futility analysis (see Section 3.5):

- Cohort I: Amyloid PET, CSF Aβ together with markers of tau pathology and neuronal activation.
- Cohort II: Brain atrophy (volumetric MRI), CSF Aβ, together with markers of tau pathology and neuronal activation.

In addition, it is anticipated that changes in AD biomarkers over time, in combination with positive findings on a primary clinical outcome may provide information regarding the potential of either treatment to modify the course of the disease.

Furthermore, biomarker data would potentially allow assessment of the effects of CAD106 and CNP520, respectively, vs. placebo on preclinical staging progression using the research criteria for preclinical AD proposed by the Preclinical Working Group of the National Institute on Aging (NIA) and Alzheimer's Association (AA) (Sperling et al 2011). The NIA-AA criteria for preclinical AD propose ordered stages for cognitively normal individuals with abnormal amyloid markers (stage 1), abnormal amyloid and neuronal injury markers (stage 2), and abnormal amyloid and neuronal injury markers and subtle cognitive changes (stage 3).

Safety considerations

In terms of safety, amyloid-based immunotherapies (particularly monoclonal antibodies such as bapineuzumab), have been associated with micro-hemorrhages in preclinical models and increases in Amyloid Related Imaging Abnormalities (ARIA) – both vasogenic edema (ARIA-E) and micro-hemorrhages (ARIA-H) - in humans. These findings appear to occur at a higher incidence in participants carrying the APOE ε4 allele and occur most frequently in HMs. Additionally, in untreated participants, APOE ε4 has been linked to development of cerebral amyloid angiopathy (CAA), which is a risk factor for spontaneous ARIA-like phenomena (vasogenic edema) and micro-hemorrhages (Kinnecom et al 2007, Oh et al 2004, Poels et al 2011, Vernooij et al 2008, Goos et al 2010). BACE inhibitors such as CNP520 might have potential to reduce vascular amyloid load and to therefore have beneficial effects on CAA. Appropriate monitoring with T2/fluid-attenuated inversion recovery (FLAIR) and T2* Gradient Echo (GRE) MRI sequences will be implemented to monitor these potential imaging events in both cohorts with actions to be followed by the investigators described in Section 13. The appropriateness of safety evaluations for each compound is described in Section 6.5.9.

A 12-month Genetic Disclosure Follow-up period was established to assess psychological and behavioral impact of disclosure of APOE genotype (Green et al 2009).

3.3 Rationale for dose, regimen, route of administration and duration of treatment

Based on the mechanism of action of the investigational drugs, no short-term benefit is expected, particularly in this preclinical stage. It is expected that if the investigational drugs delay the underlying pathological or pathophysiological disease processes, these changes will emerge only gradually over time. As discussed in the EMA Guideline on the Clinical Investigation of Medicines for the Treatment of Alzheimer's Disease and other Dementias (January 2018) prevention trials require long treatment durations, typically of at least 5 years. In this study, participants will be treated for at least 60 months (5 years) up to a maximum of 96 months (8 years), and no longer than the time until the target number of events for the TTE endpoint has been observed and confirmed in the respective cohort. This longer-than-usual treatment duration addresses the current understanding of intervention in the AD prevention setting and generates long term safety data for both compounds.

The minimum treatment duration of 60 months was chosen based on the likelihood of detecting (1) sufficient number of events and (2) sufficient cognitive decline as measured by APCC test score in the placebo arm to allow the detection of clinically meaningful treatment effects on the primary endpoints. Prolonging treatment beyond 60 months until a maximum of 96 months in initially recruited participants will allow for collection of sufficient number of events to test the primary study hypothesis, while also capping the participation in the study for all participants. Safety data collected during the study will be summarized in a blinded manner in the annual IB updates submitted to EC and Health Authorities to support continuation of treatment (e.g. IB updates will be classified as Substantial amendments for reporting purposes in the EU). Outcome and decisions from the DMC based on the interim analyses will also be described in the IB updates. Any corresponding changes to study design, including required safety monitoring, will be submitted for approval as a protocol amendment.

The two investigational treatments will be administered using different routes of administration (intra-muscular (i.m.) vs. oral (p.o.) and frequency (quarterly vs. daily). Each cohort will be fully blinded by using a matching double-blind placebo.

CAD106

Cohort I will include a single dose regimen of CAD106 450 µg with Alum 450 µg administered quarterly i.m., with the second injection administered at week 7 (6 weeks after the first injection).

Different doses and dosing regimens were evaluated in the Phase I (CCAD106A2101) and Phase II (CCAD106A2201, 2202, 2201E1, 2202E1 and 2203) studies conducted to date (for further information, refer to CAD106 IB).

The objective of the previous CAD106 dose and regimen finding studies was to identify a suitable CAD106 + adjuvant combination to induce Aβ-IgG titers in the majority of the participants, with acceptable safety and tolerability profile. The combination of CAD106 450 µg with Alum 450 µg administered quarterly i.m. was identified as the best regimen associated with strong and persistent Aβ-IgG response and suitable tolerability profile for long-term clinical studies of active immunization against Aβ (see Section 3.6).

Previous studies were not powered to evaluate clinical efficacy, however biomarker evidence of CNS activity was observed as changes on amyloid load (i.e. correlation of plaque reduction with higher antibody titers) and neurodegeneration markers, (refer to Section 3.6 and IB). The relationship of biomarker changes to clinical outcomes is unknown, but current assumption is that the greater the Aβ reduction, the greater the clinical efficacy of CAD106.

Since IgG generation and affinity maturation will require repeated injections, the onset of efficacy is expected to be 3-6 months later than with monoclonal antibodies. The effects of antibody response to CAD106 vs. placebo are measured by the change from Month 6 to Month 60 in the APCC test score and in CDR-SOB.

CNP520

Cohort II will include a single oral dose regimen of CNP520 50 mg once daily or the selected LDR if activated. The 50 mg daily dose was initially chosen due to the expected positive risk/benefit in APOE4 HMs based on the current data at that time.

The initial targeted dose of 50 mg once daily was selected based on the safety and tolerability as well as CSF Aβ lowering results obtained in the first-in-human study CNP520X2101 and the 3-month dose-ranging safety and tolerability study CNP520X2102 in healthy adults > 60 years of age. In addition, the non-clinical toxicological findings and current understanding of the physiological role of BACE-1 were considered. Based on predictions from pharmacometric modelling utilizing Phase I clinical data, the proposed dose of 50 mg achieves approximately 80% CSF Aβ lowering in 90% of the subjects. The corresponding median CSF Aβ lowering is 86%.

Genetic data suggest that a life-long 30% reduced Aβ generation is sufficient to significantly reduce the AD risk (Jonsson et al 2012). Since treatment with CNP520 will start late in life, and Aβ deposition may have already started, it was previously thought that greater inhibition will be required to demonstrate efficacy.

The non-clinical safety profile of CNP520 was studied in rats and dogs and provides adequate support for the proposed doses and duration of dosing clinically. The safety margins compared to the NOAEL provide substantial coverage for the 50 mg dose. The predicted safety margins (AUC) between the animal NOAEL and the 50 mg dose are: 8-fold (male rats; maximum dose tested (200 mg/kg/day), ≥11-fold (female rats; focal skeletal muscle atrophy without functional effects at 200 mg/kg/day) to ≥15-fold (female and male dogs; CNS effects at ≥ 30 mg/kg/day).

Lower Dose Regimen (LDR) for Cohort II

Since the start of this study, some of the other sponsors developing other BACE inhibitor compounds reported dose-dependent increases in neuropsychiatric events and early decline in cognitive performance with their compounds. These effects were seen with doses resulting in 60-80% CSF Aβ lowering, however trend for beneficial effects was observed with elenbecestat targeting 57% CSF Aβ lowering (Lo et al 2018).

Based on these results and since the median CSF Aβ lowering expected with the original dose (i.e. 86%,) is above 60%, the option for a lower dose regimen (LDR) targeting 50-60% median CSF Aβ lowering is pre-planned.

The independent DMC monitors the safety of CNP520 assessing regularly the unblinded data from the ongoing CNP520 clinical studies. If the DMC recommends a lower dose based on CNP520 safety findings and/or in light of new data for CNP520 or other BACE inhibitors, the DRM may be activated.

Based on human genetic and animal model studies (Jonsson et al 2012; Vassar et al 2014) along with the results on BACE inhibitors disclosed in October 2018 (AlzForum 2018), a 50% lowering of Aβ may be sufficient to prevent amyloid deposition and plaque formation, while maintaining a sufficient level of BACE function to avoid off-target effects that may be detrimental. In support of this, a lower level of BACE inhibition, with a dose of elenbecestat achieving 57% of CSF Aβ lowering was sufficient to show a positive trend in efficacy over

placebo (Lynch et al 2018). Therefore a dose regimen achieving a similar level of inhibition is expected to sufficiently slow the rate of further amyloid deposition, and therefore potentially delay the onset of MCI / dementia and clinical progression in people at risk of developing clinical symptoms of AD over the treatment duration of the trial.

LDR options, CNP520 dose of 6mg once daily or 50 mg once weekly, have been identified as suitable, based on PK/PD modelling based on the target population in the Generation Program. [redacted] The once a week dosing regimen is supported by the long elimination half-life of CNP520 (mean terminal half-life of 150 hours).

All proposed doses and regimens in the study (Table 3-1) are expected to show a similar range of clinical efficacy, but may have different safety profiles and hence, different benefit/risk ratios. Potential treatment effects are expected to be driven by the long-term exposure to CNP520 doses resulting in BACE inhibition of at least 50%. If the DRM is triggered, the initial, time-limited exposure to a higher dose is not expected to impact potential effect of the treatment (i.e. delay the progression to clinical symptoms).

[redacted]

3.4 Rationale for choice of comparator

Matching placebo will be used in a double-blind fashion within each cohort. The use of a placebo control is considered essential to ensure study validity and allow for appropriate assessments of safety and tolerability data as well as efficacy data. No active comparator is used in this study as there is no treatment currently available for preclinical AD.

3.5 Purpose and timing of interim analyses/design adaptations

Three types of interim analyses (IA) are pre-planned (see Section 9.6): (1) regular safety reviews by the DMC, together with immunogenicity assessments of CAD106; (2) biomarkers of CNS activity when a pre-defined number of participants reach 24 months; and (3) review of primary endpoints. An additional post-treatment IA was conducted by an independent team to assess the need for continued of the follow-up of participants after treatment termination.

The main purpose of the planned IAs will be safety monitoring and assessment of futility or overwhelming efficacy, with the potential consequence of discontinuing the respective futile active treatment arm and corresponding placebo. Safety reviews will be semi-annual, with an increased frequency as needed, to appropriately evaluate the safety/tolerability profile of the 50 mg CNP520 daily dose and the decision to maintain or activate the DRM.

The primary endpoint IA is planned to be conducted in each cohort as early as possible when a sufficient number of events is observed to assess futility.

3.6 Risks and benefits

Given the safety profile of CAD106 and CNP520 shown to date, and the positive data on amyloid pathway biomarkers, an investigation of their potential in slowing/postponing cognitive decline in pre dementia stages of AD disease offers potentially important benefits.

The overall risk to participants in this study is expected to be low due to extensive precautions and safety monitoring planned to ensure the safest possible testing of CAD106 and CNP520.

Overall, based on available non-clinical and clinical safety data, potential risks are considered manageable by applying appropriate safety monitoring as well as eligibility and discontinuation criteria.

In addition, all available unblinded safety data will be regularly review by an independent DMC.

Genetic Disclosure

Use of standardized genetic counseling protocols for the disclosure of APOE genotype has been found to be safe and well-tolerated (Green et al 2009, Green et al 2014). Data from the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) program support the psychological safety of disclosing APOE genotype using standardized genetic counseling talking points.

Although the disclosure of APOE genotype results to REVEAL participants did not result in significant short-term untoward psychological effects, individuals with high levels of emotional distress before undergoing genetic testing were more likely to have emotional difficulties after disclosure (Green et al 2009, Green et al 2014).

Therefore, this current study has specific criteria to exclude participants whose scores on pre-screening assessments indicate lack of psychological readiness to receive APOE genotype results. All HM participants who receive disclosure of their APOE genotype in this study will be followed for 12 months (consistent with the REVEAL program) to monitor the longer-term untoward psychological effects. Additionally, genetic counseling with standardized talking points is required with the actual disclosure in the study.

CAD106

CAD106 has been administered to 206 patients with predominantly mild dementia due to AD in four double-blind, placebo-controlled studies or their extensions. Data collected so far in mild AD patients is considered to be relevant to the preclinical APOE4 HM population that will be recruited in this study since the populations are expected to be comparable in terms of age ranges, concomitant conditions, amyloid positivity and genetic risk factors.

In the completed studies, patients were, on average, followed for 16 months. Following completion of these studies, the study site staff contacted patients every three months during the 2 years after their last study visit for occurrence of serious adverse events (SAEs), which were to be reported independently of a relationship to investigational drug. The median number of injections of CAD106 was six per patient, resulting in a total of > 1200 injections. Across all studies, CAD106 showed an acceptable safety and tolerability profile to support long-term dosing. Local pain (75.8%), redness (61.4%), and swelling (56.2%) were the most frequently reported local reactions, while fatigue (56.2%) and myalgia (51%) were the most frequently reported systemic reactions with CAD106. These reactions were generally mild or moderate and lasted for less than 7 days. Addition of the adjuvant Alum to CAD106 450µg improved tolerability compared to CAD106 450µg without adjuvant, in particular in respect to systemic reactions including fever.

There are minimal safety concerns for the use of Alum as adjuvant with CAD106 or with placebo. Aluminum-containing adjuvants have been used for more than 70 years in billions of doses of vaccines, and have an excellent safety record (Butler et al 1969, Edelman 1980, Jefferson et al 2004). Alum doses used for this study are half of the levels used in infants in first year of life (approximately 2 mg Alum/year in the API015 study).

CAD106 was not associated with meningoencephalitis, adverse immune reactions, or deaths. Based on the currently available data, the risk for ARIA for CAD106 is considered to be low compared with other immunotherapies.

CAD106 has not been associated with significant risk of ARIA in animals or humans. In AD patients, out of whom the great majority had amyloid pathology, only asymptomatic ARIA findings were observed.

A total of ten cases of asymptomatic ARIA were reported across 186 patients from the phase II studies. A total of 9 cases of ARIA-H were observed, of which eight patients (8/160, 5.0%) were on CAD106, while one patient (1/26, 3.8%) received placebo prior to the MRI scan with the finding. Among patients on CAD106, incidence of asymptomatic ARIA-H appears not to be APOE4 gene-dose dependent (APOE4 homozygotes 1/24, 4%; APOE4 heterozygotes 5/67, 8%; non-carriers 1/38, 2%; missing genotype 1/24, 4%).There was only a single case of asymptomatic ARIA-E in patient receiving CAD106 (1/160, 0.6%).

Explorations of biomarker data, obtained from continuous exposure over 18 months to CAD106- induced antibody titers, were largely consistent with the expected effects of an Aβ-immunotherapy. Serum Aβ IgG titer AUC correlated with longitudinal decreases in brain amyloid load over a 78 week period, as measured by florbetapir PET.

Participants and investigators are required to be alert to signs and symptoms related to CNS disorders. Clinical study protocol incorporates multiple precautions to ensure the safest possible testing of CAD106. Particular attention is paid to diagnosing clinically manifest meningoencephalitis and other severe autoimmune reactions, but also to monitoring of any not clinically apparent findings that might raise safety concerns.

Additional details are summarized in the CAD106 IB.

CNP520

The safety and tolerability of CNP520 has been assessed in 422 subjects across four Phase I studies and one Phase IIa study with three-month exposure duration. A total of 335 subjects were exposed to CNP520 and 87 to placebo. The studies included mainly healthy volunteers, from which a majority were ≥ 60 years of age. The single maximum tolerated oral dose of 750 mg identified in healthy adults appeared to be safe and well tolerated in healthy subjects ≥ 60 years of age. Multiple oral doses up to 300 mg q.d. (maximum dose tested) over 2 weeks and up to 85 mg q.d. (maximum dose tested) over 3 months appeared to be safe and well tolerated.

Across completed studies, the adverse event (AE) incidence was similar for CNP520 versus placebo both in adults and subjects ≥60 years. Most AEs were mild, not suspected to be study-drug related and resolved. No dose-dependent AEs were identified.

In Study CCNP520X2102, with the longest exposure duration so far (i.e. 3-month exposure in subjects ≥60 years of age), there was no indication for an imbalance in AE incidence between CNP520 and placebo in any of the SOCs except for skin and subcutaneous tissue disorders that occurred at a higher incidence on CNP520 than on placebo (18.0% vs. 4.2%) with no indication of dose dependence. Each of these events was mild and transient except for a single subject with generalized pruritus of moderate severity leading to discontinuation on CNP520 85 mg. There were no clinically relevant alterations of laboratory, vital signs, ophthalmological assessments (visual acuity/field) or ECG data or any indication for systematic changes over time or as a function of dose.

There was also no indication for impaired neurological function during the study and after follow-up, based on routine neurological examination and monthly cognitive testing with the Cogstate computerized battery. However, one subject on 85 mg discontinued the study due to an AE of amnesia. Narratives for the AEs leading to discontinuation are provided in the IB. Data from monthly dermatological assessments performed by a dermatologist did not raise any safety concern. In particular, there was no indication for hypopigmentation over time.

A pooled concentration-effect analysis of Holter- and 12-lead-ECG QT data from the first-in-human study (CCNP520X2101), the 3-month safety and tolerability study (CCNP520X2102) and the Japanese ethnic sensitivity study (CCNP520X1101) was performed. Results did not indicate any relevant QT prolongation by CNP520 (Refer to IB).

Based on currently available clinical safety data, there are no identified risks for CNP520. Potential or theoretical compound and class risks are based on non-clinical toxicology findings, safety observations in the current clinical program and non-clinical or safety findings reported in publications with reference to other BACE-1 inhibitor programs.

Good Laboratory Practice (GLP) embryo-fetal development studies for CNP520 have been completed and CNP520 has demonstrated neither genotoxicity nor teratogenicity; therefore, use of a condom is no longer required during intercourse for male participants who have female partners of child-bearing age.

Based on Drug-Drug-Interaction (DDI) study results it is expected that concomitant administration of strong CYP3A4 inhibitors or strong CYP3A4 inducers will affect CNP520 exposure. Restrictions or prohibited concomitant medications are described in Section 5.5.8.

Biomarker results in human studies suggest that CNP520 may itself be a weak inducer of CYP3A4. Based on *in vitro* and *in vivo* (4β-hydroxycholesterol levels in Healthy Volunteers) data, exposure to concomitant medications that are CYP3A4 substrates may be reduced when treatment with CNP520 is initiated. However, importantly, the effect of potential auto-induction on systemic exposure of CNP520 is not considered to be clinically relevant since there was no decrease in exposure to CNP520 over 3-month treatment.

No efficacy data have been generated to date. However, pharmacodynamic data has been obtained. In healthy subjects ≥60 years of age, CNP520 reduced CSF Aβ concentrations in a dose-dependent manner by up to approximately 80% at the maximum single dose tested (750 mg) and 95% after multiple dosing at the highest dose tested (300 mg q.d.). $A\beta_{40}$ concentrations in CSF decreased by 91 % compared to baseline after 3-month exposure at CNP520 85 mg q.d. Similar changes in $A\beta_{40}$ concentrations in CSF after CNP520 administration were obtained for carriers of the APOE ε 4 allele vs. non-carriers. Additional details are summarized in the CNP520 IB.

Given the safety profile of CNP520 shown to date and the positive data on amyloid pathway biomarkers, an investigation of its potential in slowing/postponing progression to cognitive symptoms in pre-clinical AD stages of the disease offers potentially important benefits.

Two compounds from other companies with the same main mechanism of action as CNP520, i.e. BACE inhibition, were associated with an increase in neuropsychiatric symptoms, along with a decline in performance on tests of memory and other aspects of thinking starting in the first three to six months of their respective studies (Egan, et al 2018, Romano, et al 2018). The doses utilized lowered CSF Aβ by 60%-80%. One other BACE inhibitors did not report these effects in small studies with doses targeting 60% and 90% Aβ lowering and one compound showed trend towards efficacy in a Phase II study using a dose achieving a 57% CSF Aβ lowering (Lo et al 2018; Lynch et al 2018). These four compounds and CNP520 have different physicochemical properties (e.g. BACE1/2 selectivity) and were studied in different populations or disease stages. (AlzForum 2018).

At this point in time, these effects have not been observed with CNP520. Prior studies with CNP520 in healthy elderly volunteers with a 3-month duration did not show any negative impact on memory or thinking tests.

The Generation studies (current study and CCNP520A2202J study) focus exclusively on APOE4 carriers (exclusively homozygotes in this study) who may benefit more from CNP520 based on their higher risk for progression to symptomatic stages of AD. Presence of the APOE4 allele has been linked to increased amyloid-β secretion and to an earlier onset of amyloid deposition (Huang et al 2017). Treatment with a BACE inhibitor may therefore be more effective in APOE4 carriers, compared to non-carriers, in whom amyloid load may be increased by other mechanisms, such as reduced clearance (Mawuenyega, et al 2010).

The hypothesis that BACE inhibition could slow or delay AD progression in preclinical stage may hold true through the early stages of the pathophysiological changes, even if a symptomatic decline in cognition is seen upon treatment initiation. Both effects may co-exist based on the potential disease modifying mode of action (preventing amyloid production) along with potential CNS side-effects (symptoms of neurological or psychiatric disorders). The clinical relevance of the decline in cognitive performance in other BACE inhibitor studies is not fully understood, but appears to be distinct from a worsening of AD progression. For this assessment, follow-up data in addition to the details of the trials with the other BACE inhibitors along with their respective biomarkers of neurodegeneration will need to be assessed as results become available.

The overall risk to participants in this study is expected to be low and acceptable due to the strong scientific rationale for the approach, the lack of alternatives to delay the onset of symptoms of Alzheimer's disease in a population at high risk, and the precautions and safety monitoring planned during treatment with CNP520. Based on available non clinical and clinical safety data, potential risks are considered manageable by applying appropriate safety monitoring as well as eligibility and discontinuation criteria. Nonetheless, there may be yet unidentified risks to CNP520 and these could potentially be serious.

In addition, all available unblinded safety data will be reviewed regularly by an independent DMC. The addition of cognitive and neuropsychiatric assessments at Month 3 will allow early detection of a decline in cognition and/or occurrence of psychiatric symptoms, if any, as seen for some but not all other BACE inhibitors. The DMC will review all data relevant for such evaluation at an increased frequency. Should the DMC conclude that the current dose does not provide a favorable benefit/risk profile, they will recommend to lower the dose which is one of the criterion for activation of the DRM. The recommendation from each DMC meetings are shared with Health Authorities and any recommendation impacting the study design as a consequence from a safety signal will be shared with all parties without delay.

In case of DRM activation, and to protect participants from further exposure to the original higher doses, the LDR will be implemented according to the process described in the DRM Notification document. For sites or countries where the protocol v05 has not yet been approved by regulators at the time of DRM, the switch to the LDR may be managed through the Urgent Safety Measure process.

4 Population

4.1 Pre-screening Epoch and Genetic Disclosure Follow-up

Prior to the Genetic Disclosure visit, participants must meet the Pre-screening eligibility criteria. Medical history, including concomitant medications, will be assessed during an interview with the participant. The same criteria will then be reviewed against the participant's medical records by the Investigator during Screening.

4.1.1 Inclusion criteria

1a. Written informed consent (Informed consent #1) obtained before any assessment is performed, including consent to receive disclosure of their APOE genotype

2a. Male or female, age 60 to 75 years inclusive, at the time of signing Informed consent #1 (same age restriction also applied at Informed consent #2).

- Once the cap of approximately 20% of total participants in the age group 60-64 years at time of signature of ICF#2 is met, a restriction to this age group will apply.
- Note: the same age limitations of 60-75 years, inclusive is also applied at the time of signing Informed consent #2

3a. 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 (see Section 4.2).

4a. Mini-Mental State Examination (MMSE) total score ≥ 24 (can be based on documented result obtained within the previous 3 months).

5a. Psychological readiness to receive APOE genotype information based on pre-disclosure rating scales, specifically:

a. Geriatric Depression Scale (GDS) total score ≤ 6.
If the score is between 7 and 10 (inclusive), the participant can only be included based on investigator's judgment, with special attention given to 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 or19, the participant can only be included based on the investigator's judgment.

6a. Participant is 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).

7a. Participant's willingness to have a study partner for the Screening and Treatment epoch (see Screening and Treatment Epoch Inclusion criteria #6 below).

4.1.2 Exclusion criteria

1a. Any disability that may prevent the participant from completing all study requirements (e.g., blindness or deafness that is not appropriate for age, severe language difficulty, etc.).

2a. Current medical or neurological condition that might impact cognition or performance on cognitive assessments e.g., MCI, dementia, Huntington's disease, Parkinson's disease, Lyme disease, syphilis, schizophrenia, bipolar disorder, active major depression, attention-deficit / hyperactivity disorder (ADD / ADHD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), active seizure disorder, alcohol/drug abuse or dependence currently, or dependence within the last two years, history of traumatic brain injury with loss of consciousness and ongoing residual transient or permanent neurological signs/symptoms including cognitive deficits, and/or associated with skull fracture.
Note: the available Investigator Guide provides guidance on the interpretation of laboratory tests for Lyme disease.

3a. 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 or HIV infection (based on a positive lab result for HBV/HCV and/or HIV, to be performed during screening if not available from the last 12 months), severe renal impairment, severe hepatic impairment, uncontrolled or significant cardiac disease including recent (within six months) myocardial infarction, congestive heart failure (New York Heart Association [NYHA] functional class III-IV), unstable angina, or long QT syndrome.
Note: the available Investigator Guide provides guidance on the interpretation of laboratory tests for HBV and HCV.

4a. 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.

5a. History of hypersensitivity to any of the investigational drugs or their excipients/adjuvant, or to drugs of similar chemical classes.

6a. Indication for or current treatment with ChEIs and/or another prescription AD treatment (e.g. memantine).

7a. Contraindication or intolerance to MRI or PET investigations (with fluorinated radioligands).

4.2 Screening, Treatment and Follow-up Epochs

4.2.1 Inclusion criteria

Participants eligible for inclusion must fulfill all of the following criteria prior to randomization:

1b. Written informed consent (Informed consent #2) for participation to the Screening, Treatment and Follow-up Epochs (Participant must still be between 60-75 years, inclusive, at the time of signing Informed consent #2; after reaching the maximum of 20% in the younger age group of 60-64 years, only those 65-75 years will be eligible)

2b. 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, including continued psychological readiness for participating in the study as determined by clinical judgment.

3b. Homozygous APOE4 genotype.

4b. Cognitively unimpaired as defined by:

At screening visit, score of 85 or greater on the RBANS delayed memory index score AND global CDR score of 0 with two exceptions:

a. 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 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 investigator judges that cognition is unimpaired following review of the MCI/dementia criteria.

5b. 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.

6b. Study partner, who spends sufficient time with the participant, and agrees to participate in the study must have an adequate functioning (e.g., intellectual, visual, and auditory) and be fluent in, and able to read, the language in which study assessments are administered. (see definition in Appendix 4)

Additionally the study partner must be capable of and willing to:

- Accompany the participant to all required twice yearly visits
- Meet the definition of a "study partner" as described in Appendix 4.

4.2.2 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 to the use of treatment requiring a specific time window prior to randomization, can be re-screened at a later stage.

1b. 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 (score of 3 on the Wahlund's scale in 2 or more bilateral brain regions), recent stroke, recent cerebrovascular disease evidenced by more than one lacunar infarct ≤ 20 mm or any single infarct > 20 mm, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformation, subdural hematoma or space-occupying lesions).

For Cohort I (CAD 106) only, in addition to the above, evidence of ARIA-H as demonstrated by:

- More than four cerebral microhemorrhages (defined as having a 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)

2b. Score "yes" on item four or item five of the Suicidal Ideation Section of the eC-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 is included in the Suicidal Behavior Section) if this behavior occurred in the past two years prior to screening (refer to Section 7.6 for management).

3b. A positive drug screen at Screening, if, in the Investigator's opinion, this is due to drug abuse or dependence. Participants with a positive drug screen not believed to be related to drug abuse or dependence (e.g. presence of prescription drugs in urine without evidence of prescription drug abuse), can be re-screened once.

4b. Significantly abnormal laboratory results at Screening as described in the Appendix 13.4 OR meeting the exclusionary alert values as specified in the Laboratory Manual, considered as clinically significant in the opinion of the Investigator. If an abnormal finding is the result of a temporary condition, the laboratory test can be repeated once.

5b. Clinically significant "active" infection which has not resolved within two weeks prior to initial dosing. In that particular case, delayed randomization may be considered.

6b. Current significant ECG findings as reported by central reader that are assessed as clinically significant by the investigator (e.g. sustained ventricular tachycardia, significant second or third degree atrioventricular block without a pacemaker, long QT syndrome or clinically meaningful prolonged QT interval). QTc interval > 500 ms is exclusionary.

7b. Use of other investigational drugs prior to screening until:

- Blood concentration has returned to Baseline (or below Serological responder threshold) for biologics, e.g. antibodies induced by active immunotherapy; or
- Within 30 days or five half-lives, whichever is the longest for monoclonal antibodies or small molecules e.g. BACE-1 inhibitors.

8b. Treatment

a. 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 (examples include, but are not limited to, clozapine, cancer medical treatments like tamoxifen, systemic immunosuppressive drugs like methotrexate and interferon or other immunosuppressive biological medicines for rheumatic diseases or multiple sclerosis.

b. in the four weeks prior to randomization and/or current treatment with any CNS active drug(s), with exceptions described in Table 5-3.

c. For Cohort I (CAD106) only, treatment with warfarin or other coumarin derivatives, or with a combination of acetylsalicylic acid and an anti-platelet agent (e.g. clopidogrel) within seven days (five half-lives) prior to randomization, or current indication for chronic treatment with a direct oral anti-coagulant.

d. For Cohort II (CNP520) only: Current chronic treatment (> 3 months) with (see Table 5-2, expanded list is available in the Investigator Guide):
   - strong CYP3A4 inducers or strong CYP3A4 inhibitors;
   - or drugs with a narrow therapeutic index known to be primarily metabolized by CYP2C or CYP3A isoenzymes, and sensitive Pgp substrates

9b. Violations of concomitant medication restrictions as described in Table 5-3.

10b. Donation or loss of 400 mL or more of blood within 8 weeks prior to screening blood sampling and/or Lumbar Puncture if applicable.

11b. Previous or planned Nuclear Medicine Radiology exposure that will exceed the dosimetry acceptable exposure in the country, when adding the scheduled study PET scans or allergy to low doses of fluorinated radioligands.

12b. For Cohort II (CNP520) only: Participants with clinically relevant depigmenting or hypopigmenting conditions (e.g. albinism, vitiligo) or active / history of chronic urticaria in the past year.

13b. For Cohort I (CAD106) only: Participants with previous organ transplantation or stem cell transplantation.

Exclusion criteria for participation in the Lumbar Puncture

14b. 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 spinal conditions that in the judgment of the Investigator would preclude a lumbar puncture.

No additional exclusions may be applied by the Investigator in order to ensure that the study population will be representative of all eligible participants.

5 Treatment

5.1 Investigational treatment

5.1.1 Cohort I

CAD106:

- CAD106 will be available as a white lyophilizate powder for reconstitution. Each vial of CAD106 individual vials contain the equivalent of 0.5 mg of CAD106, extractable after reconstitution.
- Alum as adjuvant will be provided as a separate medication pack.

Prior to administration, CAD106 lyophilizate will be reconstituted with sterile water for injection and mixed with the provided vial of Alum.

Placebo:

- Placebo will consist of a lactose powder with same appearance as CAD106 lyophilizate.

- Alum as adjuvant will be provided as a separate medication pack.

After reconstitution with the same volume of sterile water for injection, the placebo vial will present with the same appearance and viscosity as the reconstituted CAD106 solution.

Prior to administration, the reconstituted placebo will be mixed with the provided vial of Alum.

CAD106 with Alum and placebo with Alum are to be prepared by a Pharmacist or appropriate delegate, as described in the Medication Manual.

Sterile water for injection for placebo and CAD106 reconstitution will be purchased locally.

All study treatments, including placebo, must be stored according to the storage conditions specified on the medication labels and in accordance with regulations governing investigational medicinal products and local regulations. Detailed instructions will be provided in the Medication Manual.

5.1.2 Cohort II

CNP520

CNP520 50 mg for oral administration once daily will be provided as capsules in separate bottles supplied for at least 3 months of treatment. An overage is included to account for the permitted treatment windows.

In case of DRM, new study medication and/or alternative investigational drug packaging will be made available. The sites, EC/IRBs and HAs will be notified of the DRM activation and the selected LDR as described in the DRM Notification Document. Instructions for sites to notify the ongoing participants and the new dispensing instructions, timelines and process to implement will be described in the DRM Notification Document.

- An interim dispensing to once weekly regimen for all treatment arms using the currently dispensed medication packs may be implemented until updated LDR medication packs are available at sites.

Matching placebo will be provided as capsules in separate bottles supplied for at least 3 months of treatment. An overage is included to account for the permitted treatment windows.

All study treatments, including placebo, must be stored according to the storage conditions specified on the medication labels (below 25°C) and in accordance with regulations governing investigational medicinal products and local regulations.

5.1.3 Additional study (procedural) treatment

Other study treatments include:

- an amyloid PET tracer (e.g. ^{18}F-florbetapir, ^{18}F-Flutemetamol, or ^{18}F-Florbetaben according to local regulation (e.g. in Germany, only the commercially available amyloid tracer florbetaben) will be used and
- a tau PET tracer (^{18}F-flortaupicir (AV-1451), MK-6240 or PI-2620), voluntary for a subset of site that have access to the tau tracer, imaging capabilities and where locally permitted (i.e. not in Germany; applicable for USA and Canada with flortaucipir only)

- [redacted]

Further information can be found in the respective Investigator Brochure for the selected tracer(s) in the country or Summary of Product Characteristics (drug labelling information if approved in the country), will be provided to the sites and submitted to Institutional Review Boards (IRBs)/ Ethics Committees (ECs) and Health Authorities (HAs), as appropriate.

5.2 Treatment arms

The study consists of two cohorts with a total of four treatment arms.

Participants will be assigned to one of the following four treatment arms in a ratio of 5:3 in Cohort I and 3:2 in Cohort II.

The IRT (Interactive Response Technology) system will take into account the cohort-specific exclusion criteria. The IRT will assign participants across cohorts in parallel, applying the appropriate ratio, and will also account for any applicable cohort specific exclusion criteria and concurrent completion of cohort allocation (including pause in allocation to Cohort I (see Section 3.2)). Participants eligible to both cohorts will not be offered the opportunity to choose one of the two cohorts.

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.

Participants will be given i.m. injections at Weeks 1, 7, 13 and quarterly i.m. injections (approximately every 13 weeks) thereafter, until the last injection 3 month prior to completion of the Treatment Epoch, e.g. for the last participant the last injection will be administered at Month 57.

Cohort II (CNP520 and placebo)

Arm #3: CNP520 50 mg capsule for once daily oral (p.o.) administration; or CNP520 LDR if DRM is activated

Arm #4: Placebo to CNP520 50 mg capsule for once daily oral (p.o.) administration; or placebo to CNP520 LDR if DRM is activated. If DRM is activated:

All participants already assigned to Arm #3 will be transitioned from CNP520 50 mg daily to the selected LDR (either 50 mg capsule for once weekly oral (p.o.) administration or 6 mg capsule for once daily oral (p.o.) administration).
All participants already assigned to Arm #4 will be transitioned to matching Placebo for LDR.

5.3 Treatment assignment, randomization

At Visit 301, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the available treatment arms. The Investigator or his/her delegate will contact the IRT after confirming that the participant satisfies all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number(s) for the package of investigational drug to be administered (Cohort I) or dispensed (Cohort II) to the participant. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. The corresponding separate medication list will be produced by, or under the responsibility of Novartis Drug Supply Management, using a validated system that automates the random assignment of randomization numbers to investigational drug packs containing each of the investigational drugs.

The randomization scheme for participants will be reviewed and approved by a member of the Novartis Randomization Office.

In total, in Cohort I, about 690 eligible participants will be randomized via IRT to one of the two treatment arms. This will be implemented via central randomization to achieve a ratio of 5:3, CAD106 vs. placebo. A total of approximately 650 participants will be randomly assigned centrally into Cohort II with a ratio of 3:2 CNP520 vs. placebo.

Participants who are eligible for both investigational drugs will be randomly assigned to one of the two cohorts in a 1:4 ratio favoring recruitment to Cohort II; this randomization ratio will be active until approximately 65 participants have been randomized in Cohort I. At that time, allocation will shift to Cohort II only (thus changing the allocation ratio between cohorts from a 1:4 ratio to a 0:5 ratio until approximately 650 participants in total are randomized in Cohort II). Upon positive results from the CNS activity IA on Cohort I, allocation into Cohort I may resume until the remaining participants required for Cohort I (approximately 690 in total) are randomized. Randomization ratio would recommence at 1:4 ratio. However, at the time of futility analysis, it is anticipated that recruitment to Cohort II would be complete; if this is the case, then allocation would be then be solely into Cohort I. Upon assignment to a cohort, the participant will be randomized to one of the two treatment arms (active or placebo) in that cohort. New participants who are eligible for only one of the two cohorts will be randomly assigned via IRT to one of the two treatment arms in the corresponding cohort. Randomization across the cohorts will be implemented via central adapted randomization such that the cohort specific randomization ratio will be achieved.

Randomization will be stratified by age group (60 to <65 and ≥65) and region (North America/other, Europe). Region is known to be a surrogate of many measured and unmeasured factors and is chosen as stratification factor for randomization to optimize balance of potential prognostic factors. Rationale for stratifying by age group is provided in Section 3.2.

Note: The stratification by age is using age at randomization, not age at screening. Participants who were 75 years old at screening and reached age 76 at randomization due to the long screening time are still eligible and will be randomized into age stratum ≥65.

5.4 Treatment blinding

Participants, site personnel, and data analysts will remain blind to the identity of the treatment within each cohort from the time of randomization until database lock using the following methods:

Randomization data are kept strictly confidential until the time of database lock and will not be accessible by anyone else involved in the study with the following exceptions:

- Authorized independent bioanalysts, programmers, statisticians, and data managers in charge of the antibody titers for CAD106 [redacted], not otherwise involved in the daily study management activities.
- DMC members and unblinded statisticians and programmers in charge of the interim DMC outputs and Interim analyses (including statisticians from external vendors involved in data analyses).
- Key sponsor personnel reviewing group-level outputs from post-treatment data pooled across the two Generation studies at post-treatment IA. This additional analysis (see Section 3.5) was conducted by the same independent statistical team

Further details for each of the personnel involved in data collection or reporting are presented in Table 5-1.

Table 5-1 Blinding status up to database lock

Groups involved in the Study	Access to Randomization list
Participants, study partner, site personnel	No (blinded)
Sponsor and CROs involved in the study conduct	No (blinded)
Progression Adjudication Committee (as per charter)	No (blinded)
*Participant eDiary vendor, Analysts at T-cell activation assay laboratory, AD biomarker analysts, PET analyst at the Imaging CRO, pharmacist	No (potential to unblind unless futility at any IA)
Analysts in charge of antibody titer (Cohort I) [redacted] (Cohort II)	Yes (unblinded)
Drug Supply Management (including IRT provider)	Yes (unblinded)
DMC (as per charter) and independent statistical team	Yes (unblinded)
Key sponsor personnel	Partially (only group-level and pooled across the 2 studies for CNP520 only)

*The data with a potential to unblind recipients (typically markers of the treatment effect) will be stored in a restricted area of the database until database lock. Although the randomization list will NOT be communicated to them, the following personnel will be considered as unblinded due to the results post-baseline:

- Participant diary vendor (tolerability data in Cohort I)
- Analysts at T-cell activation assay laboratory (Cohort I)

- AD biomarker analysts (Aβ, Total-tau and Phospho-tau in CSF and Aβ in plasma, NFL in blood and CSF)
- PET and MRI analyst at the Imaging CRO (Amyloid, Tau, [redacted] volMRI scans)

Within each cohort, treatment packaging, labeling, schedule of administration, appearance, taste, and odor will not differentiate active study medication from placebo.

- The identity of the CAD106 treatment is protected by providing a matching placebo powder of same appearance requiring the same reconstitution and mixing procedure. After reconstitution, the CAD106+Alum solution will have a same appearance (color and viscosity) as the matching Placebo+Alum. However, during the process of reconstitution, full blinding may not be possible for the pharmacist (or appropriate delegate); therefore the pharmacist should remain independent from other study activity to maintain the blinding for the study.
- The identity of CNP520 will be concealed by the use of an identical matching placebo capsule and similar packaging.

Unblinding will only occur in case of participant emergencies (see Section 5.5.11), and at the conclusion of the study.

All other data with potential for unblinding (as for instance tolerability data) will be treated similarly as randomization data with regards to blinding: the data will be loaded into a restricted area. Access will only be granted to members of the authorized independent unblinded team.

In the case that CAD106 meets the futility analyses criteria, data for Cohort I participants will no longer be treated as restricted, to allow for monitoring of the antibody titer levels needed to assess timing of re-randomization (Refer to Section 5.5.9)

5.5 Treating the participants

5.5.1 Participant numbering

Each participant is uniquely identified in the study by a combination of his/her center number and participant number. With the addition of the preliminary genotyping step (ICF#1A), the participant ID assigned at this step may be kept throughout the study or may be changed at ICF#1B for the remainder of the study.

Upon signing the Informed consent #1B for the Pre-screening Epoch and Genetic Disclosure Follow-up, the participant ID must be used as described below: the center number is assigned by the sponsor to the investigative site, and the participant is assigned a participant number by the Investigator.

The Investigator or his/her staff will contact the IRT and provide the requested identifying information for the participants to register them into the IRT before randomization (i.e. at Visit 201 (Screening Visit). The site should select the Case Report Form (CRF) book with a matching Participant Number from the Electronic Data Capture (EDC) system to enter data.

Once assigned to a participant, any participant number will not be reused, regardless if used under preliminary genotyping or pre-screening. If the participant fails to be randomized in the Treatment Epoch for any reason, IRT must be notified that the participant was not randomized. The reason for not being randomized will be entered on the Screening Epoch Study Disposition CRF, and the Demography eCRF should also be completed.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied with the investigational treatment in packaging of identical appearance by cohort.

A unique medication number is printed on each part of this label which corresponds to one of the four treatment arms. The study site personnel will identify the study drug package(s) to dispense to the participant by contacting the IRT at Baseline (randomization).

Further calls to IRT are required for re-supply at each of the 3-month visits to obtain the medication number(s) and identify the pack(s) to be dispensed. If participant has suspended study treatment, the call to IRT is still required to indicate the visit occurred but no drug was dispensed.

Upon DRM, a new set of supplies may be provided for replacement.

5.5.3 Handling of investigational treatment, exposure and compliance

Investigational treatment must be received by a designated person at the study site, handled and stored safely in a temperature controlled environment, according to label requirements, and kept in a secured location, to which only the Investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the appropriate Sponsor Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the participants, except for the medication number.

The Investigator or designee must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits, and at the completion of the trial. Participants allocated to Cohort II (CNP 520 or matching placebo) will be asked to return all unused investigational treatment and packaging at each study visit and at the end of the study, or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the site monitor or to the address provided in the Investigator file at each site.

Compliance will be assessed for study participants in Cohort II by the Investigator and/or study personnel at each visit as described above.

5.5.4 Instructions for prescribing and taking investigational treatment

Cohort I (CAD106 or placebo)

A Pharmacist, or qualified person for handling medication as per local law, will perform the reconstitution of the CAD106 lyophilizate or matching placebo powder with water for injection, and mixing of the reconstituted solution with Alum according to the treatment arm assigned by central randomization, and managed via IRT.

Detailed guidance for reconstituting the CAD106 lyophilizate, mixing with adjuvant, preparing and injecting the investigational drug will be provided in the Medication Manual.

The Pharmacist will provide the reconstituted syringe with the assigned study medication to the Study Nurse for i.m. injection to the participant. The total volume injected for the 450 µg dose of CAD106 or placebo with Alum 450 µg will be of 0.90 mL per injection.

Each participant is scheduled to receive at most 33 i.m. injections of CAD106 or placebo with Alum, at Baseline, weeks 7, 13, 26, and quarterly thereafter until the last injection 3 months prior to completion of Treatment Epoch.

Study medication administration will take place under ambulatory conditions at the study center. The study drug must be administered where emergency resuscitative equipment and personnel trained in the management of anaphylaxis are immediately available to treat any systemic reactions under the direct supervision of a physician. The injection will be performed intramuscularly on the upper arm or gluteus. The location of each injection should alternate from the previous injection. Details of the injection (date, time, and location) will be entered on the Drug Administration Record pages of the eCRF.

Prior to the first injection at Baseline, all inclusion/exclusion criteria will be checked by the Investigator. Prior to each of the following injections, the pre-dose assessment results (physical/neurological assessments, vital signs, laboratory test, and last MRI results) will be reviewed. In case of fever or abnormal findings, the injection should be postponed as specified in Section 5.5.5. In case of SAEs (see Section 13), the Investigator will conduct additional appropriate investigations (including lumbar puncture and/or MRI, as appropriate) prior to proceeding with the next injection.

The first record into the participant eDiary will be completed at the site, before the participant leaves the study center (see Section 6.5.7), to ensure understanding and access to the eDiary.

After each injection, vital signs will be measured at 30 (±5) and 60 (±10) minutes post-dose. Thereafter, the participant will be allowed to leave the site once the Investigator or a designee with adequate clinical experience (e.g. co-Investigator, nurse), has checked the participants condition and confirmed there are no clinical findings precluding their discharge.

Cohort II (CNP520 or placebo)

Bottles of study medication CNP520 or matching placebo will be dispensed at the Baseline Visit (Visit 301). Drug will then be dispensed at scheduled visits throughout the Treatment Epoch. At each drug dispensing visit, Cohort II participants will receive the required supplies (bottles of oral medication) to cover treatment needs until the next dispensing visit, including an overage in case the subsequent visit has been delayed due to scheduling constraints.

For dispensing visit days, participants must bring their bottle(s) with them to the site (for drug accountability) and be instructed NOT to take the morning dose. Dosing on the dispensing visit days must occur on site from the newly dispensed supply, after the visit assessments are completed (especially the blood sampling). Particular attention should be taken to schedule ECGs about 2.5 hours after the drug administration (Refer to Section 6.5.5). In cases of technical hurdle (e.g. pharmacy off site drug delivery occurs in late morning) dispensing from the current in use bottle is allowed as long as it is documented and consistently implemented.

CNP520 or matching placebo is to be taken orally once a day, preferably at the same time every day, i.e. in the morning, with or without food. If dose administration is changed to once weekly, it should be taken preferably on the same day of the week, every week.

[redacted]

Once the eligibility of a participant for entry into the Treatment Epoch has been confirmed based on the study inclusion/exclusion criteria, a medication number will be assigned to the participant and the corresponding study medication will be dispensed (see Section 5.3).

5.5.5 Permitted dose adjustments and interruptions of investigational treatment

Change in frequency of dosing by site or participant is not permitted. In the case of a change in the scheduled administration of any study treatment for any reason, this change must be recorded on the Dosage Administration Record page on the eCRF.

Cohort I (CAD106 or placebo)

Investigational treatment should be suspended for participants who:

- no longer have a study partner for a period of > 3 months); when the replacement study partner is identified, study treatment can be resumed for the participant
- during the time they are taking medications listed in Table 5-2 leading to suspension of investigational treatment (e.g. for an acute condition)
- condition/decision leading to suspension of study treatment at any time for any reason (including a participant's request)

In case of vaccination (e.g. flu, herpes zoster) within two weeks of the next scheduled injection in Cohort I, the injection of CAD106 or placebo should be held until two weeks after the vaccination but no later than four weeks after scheduled injection date, in accordance with the defined allowable visit windows. Similarly, in case of fever, signs of inflammation on laboratory tests, abnormal physical/neurological examinations (including signs or symptoms of infections such as colds, urinary tract infections, cough, etc.), the injection should be postponed until recovery and no later than four weeks after scheduled injection date.

In case an injection is postponed for reasons described above, or is missed for any reason for more than four weeks after the scheduled injection date, it should be skipped and treatment should resume at the next regularly scheduled injection.

Dose adjustment of CAD106 or Alum is not permitted.

Cohort II (CNP520 or placebo)

Dose adjustments of CNP520 are not permitted by the site or participant.

In case a daily dose was omitted, it can still be taken until approximately 6 hours after the usual daily intake time, otherwise it should be skipped and treatment resumed next day at regular time.

In the case that the timing of the site visit deviates from the regular time that the participant takes the study medication, the study medication can still be administered at the site visit if it is within ±6 hours of the usual time, i.e. the dose can be given 18 to 30 hours after the previous dose.

If the DRM is activated for a weekly administration and a weekly dose is missed, it can still be taken within 3 days (72 hours) of the missed regular weekly dosing day. Otherwise, the dose should be skipped and treatment resumed at the regular day of the next week. At scheduled visits every 3-months, the weekly dose should be withheld until the site visit occurs. In case that one or more dose(s) is missed, study drug treatment should resume as soon as possible. Any missed doses must be recorded in the Dosage Administration eCRF page. Refer to Section 5.5.9 for reasons to discontinue or suspend study treatment.

Study treatment can be suspended temporarily for the following reasons:

- participant no longer has a study partner for a period of > 3 months; when the replacement study partner is identified, study treatment can be resumed for the participant
- during the time the participant is taking medications listed in Table 5-2 leading to temporary suspension of investigational treatment (e.g. for an acute condition)
- condition/decision leading to suspension of study treatment at any time for any reason
- participant's request to suspend study treatment temporarily

Study treatment can be resumed at any point later in the study after the condition above has resolved, and participant attended the scheduled visits / assessments per protocol during the duration of the suspension.

5.5.6 Rescue medication

No medication is currently available for treating preclinical AD. Following randomization, the investigator should avoid initiating a symptomatic treatment (such as ChEIs or memantine) until

progression has been confirmed as meeting criteria for dementia due to AD (McKhann et al 2011). Symptomatic treatments for AD (such as ChEIs or memantine) can be prescribed, in addition to the investigational treatment, only as per the approved label of the drug (i.e., only after the diagnosis of dementia due to AD and not during the preclinical or MCI stages). Once these medications are introduced, their dosage should not be adjusted in the six weeks preceding a clinical evaluation.

Other CNS-active medications to control behavioral changes are allowed with restrictions as specified in Table 5-3.

Use of symptomatic treatment for AD must be recorded on the Concomitant medications/Significant non-drug therapies in the eCRF.

5.5.7 Concomitant treatment

The Investigator should instruct the participants to notify the study site (by telephone and during study visits) about any new medications he/she takes after study enrollment. All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant has been enrolled into the study must be recorded on the eCRF.

Treatments in the case of meningoencephalitis

In case of occurrence of meningoencephalitis, the best medical care according to Investigator or per best local medical practice should be administered, e.g. high doses methylprednisolone (500 or 1000 mg per day) administered intravenous (i.v.) for five days, followed by p.o. administration of 100 mg/day prednisolone to be slowly reduced depending on the development of the clinical symptoms.

In case of treatment failure or rebound effects, due to lowering of the steroid dose, treatment with azathioprine, i.v. immunoglobulins (4 mg/kg body weight) or plasmapheresis/plasma exchange may be considered by the Investigator.

In cases of meningoencephalitis, investigational treatment should be discontinued (see Section 5.5.9), and PPW (premature participant(s) withdrawal) visit assessments should be scheduled when possible considering the participant's health condition.

Also refer to Section 13.1 Appendix 1 for actions required in case of meningoencephalitis.

[redacted]

[redacted]

5.5.8 Prohibited and restricted treatments

For Cohort I:

- Chronic use (> 3 months) of warfarin or other coumarin derivatives as anti-coagulants, including combination treatment with antiplatelet agents (e.g. clopidogrel) and acetylsalicylic acid is prohibited due to potential confounding effects on interpretation of potential AEs (e.g. brain hemorrhages) occurring during the study.

For Cohort II (extensive list of the drugs covered below is available as an Investigator Guide):

- Chronic use (> 3 months) of a strong CYP3A4 inducer or a strong CYP3A4 inhibitor is prohibited due to the potential effect on CNP520 exposure.
- Narrow therapeutic index drugs known to be primarily metabolized by CYP2C or CYP3A isoenzymes, and sensitive Pgp substrates are prohibited, since CNP520 may be a weak inducer of CYP3A4 and potentially of CYP2C9 and Pgp.

In addition, CNS-active drugs are generally prohibited except if listed and used within the restricted conditions specified in Table 5-3.

Table 5-2 Prohibited treatment

Cohort	Medication	Action to be taken during treatment phase
Cohort I only	Chronic use (>3 months) of warfarin or other coumarin derivatives or a combination of acetylsalicylic acid and an anti-platelet agent (e.g. clopidogrel)	Discontinue investigational treatment, continue monitoring participant at scheduled study visits until PPW or EoS
	Chronic use (> 3 months) of systemic immunosuppressive therapies such as systemic corticosteroids	Discontinue investigational treatment (no new injection), continue monitoring participant at scheduled study visits until PPW or EoS
Cohort II only	Strong CYP3A inducer (e.g. Carbamazepine, Phenytoin, Rifampicin, St John's wort)	**Acute use:** allowed, no action (continue study treatment and visits)
		Chronic use (>3 months): Discontinue investigational treatment, continue monitoring participant at scheduled study visits until PPW or EoS

Cohort	Medication	Action to be taken during treatment phase
	Strong CYP3A inhibitor (e.g. clarithromycin, grapefruit juice, itraconazole) Drugs with a narrow therapeutic index (TI) known to be primarily metabolized by CYP2C (e.g. warfarin) or CYP3A (e.g. cyclosporine, ergotamine, fentanyl) isoenzymes, and sensitive Pgp substrates (e.g. digoxin, talinolol).	**Acute use:** Suspend investigational treatment; continue monitoring the participant at scheduled study visits, resume investigational treatment upon discontinuation of the drug. **Chronic use (>3 months)**: Discontinue investigational treatment; continue monitoring participant at scheduled study visits until PPW or EoS.
Both Cohort I and Cohort II	Any drug or treatment known for its potential to cause major organ system toxicity, i.e. drugs that require monitoring of a specific organ or body fluid. Examples include but are not limited to clozapine, cancer medical treatment like tamoxifen, systemic immunosuppressive drugs like methotrexate or interferon, or other immunossuppressive biological medicines for rheumatic diseases or multiple scrlosis	Discontinue investigational treatment, continue monitoring participant at scheduled study visits until PPW or EoS
	CNS active drugs including drugs associated with abuse, e.g. methylphenidate, amphetamine, atomoxetine or modafinil, unless otherwise specified in Table 5-3	**Acute use:** Suspend investigational treatment; continue monitoring the participant at scheduled study visits, resume investigational treatment upon discontinuation of the drug. **Chronic use:** Discontinue investigational treatment; continue monitoring participant at scheduled study visits until PPW or EoS.

EoS = End of Study; PPW = Premature participant withdrawal

Parenteral immunoglobulin preparations, blood products, plasma derivatives, and certain CNS-active agents are restricted as described in (Table 5-3).

No medication is currently available for treating worsening of symptoms in preclinical AD. Following randomization, the Investigator should avoid initiating symptomatic treatments (such as ChEIs or memantine) until worsening has been confirmed as meeting criteria for dementia due to AD (McKhann 2011). Symptomatic treatments for AD (such as ChEIs or memantine) can be prescribed as per standard of care, in addition to the investigational treatment. Once these medications are introduced, their dosage should not be adjusted in the 6 weeks preceding a clinical evaluation.

Table 5-3 Restricted treatments

Cohort	Medication	Restrictions / action to be taken during treatment phase
Cohort 1 only	Vaccination (e.g. flu shot)	Postpone injection to allow 2 weeks lag from the vaccination no later than 4 weeks after scheduled injection date, in accordance with the defined visit windows
	Antibiotics or antiviral	Postpone injection according to Section 5.5.5

	Acute use of immunosuppressive therapies such as systemic corticosteroids	In case of treatment within two weeks of the next scheduled injection, the injection of CAD106 or placebo should be delayed until appropriate medication washout, but no later than four weeks after scheduled injection date, in accordance with the defined allowable visit windows.
	Parenteral immunoglobulin preparation, blood products, and/or plasma derivatives	Postpone injection according to Section 5.5.5
	Direct Oral Anticoagulants (DOAs)	Allowed if DOA dosage is adequate to control their coagulation (including appropriate prothrombin laboratory test and/or clinical judgment, as required)
Both Cohort 1 and Cohort 2	Cholinesterase inhibitors or memantine (permitted only after diagnosis of dementia due to AD and not during the preclinical or MCI stage)	If initiated during the study, maintain a stable dose in the 6 weeks prior to clinical evaluations
	Other anti-coagulants (non-coumarin related)	Other anti-coagulant treatments are allowed. However, when appropriate, review the International normalized ratio (INR) level and adjust dosage according to the prescribing information.
	Sedative hypnotics	Will be allowed if, in the opinion of the Investigator, use does not constitute abuse, does not affect cognition AND participants are currently treated with a stable regimen (defined as no change to the participant's medication intake pattern rather than adherence to the prescribed regimen) for at least 12 weeks prior to randomization. If initiated during study, maintain a stable regimen (including in the 6 weeks prior to clinical evaluation). Resting state fMRI need not be performed during MRI examinations if taken chronically. If taken as-needed, these must be withheld for 72 hours prior to cognitive assessments, FDG PET scan or/and fMRI (as applicable).
	Opioid-containing pain treatments (e.g., codeine, morphine, hydromorphone, oxycodone, propoxyphene and its variations, and combination products that contain a narcotic)	Chronic use (>3 months) is exclusionary. Acute use for temporary conditions is allowed if, in the opinion of the investigator, use does not constitute abuse and does not affect cognitive testing. Resting state fMRI need not be performed during MRI examinations unless taken as-needed. If taken as-needed, these must be withheld for 72 hours prior to cognitive assessments and/or fMRI (as applicable).

	Pregabalin, and gabapentin (when used for neuropathic pain and/or postherpetic neuralgia and/or fibromyalgia and/or restless leg syndrome) and pramipexole, ropinirole and rotigotine (when used for restless leg syndrome)	Will be allowed if, in the opinion of the investigator, use does not affect cognition (for example, because of excessive somnolence and/or dizziness) AND participants are currently treated with a stable regimen (defined as no change to the participant's medication intake pattern) for at least 12 weeks prior to randomization. If initiated during study, maintain a stable regimen (including in the six weeks prior to clinical evaluation).
	Selective serotonin re-uptake inhibitors (SSRIs, e.g. paroxetine, sertraline, citalopram, escitalopram), serotonin norepinephrine re-uptake inhibitors (SNRIs, e.g. venlafaxine, duloxetine), atypical antidepressants such as vortioxetine, antipsychotics, and low dose tricyclic antidepressants.	Will be allowed if, in the opinion of the Investigator, use does not represent an exclusionary condition (for example, active major depression) AND provided participants are currently treated with a stable regimen for at least 12 weeks prior to randomization. If initiated during study, e.g. for mood stabilization, maintain a stable regimen in the 6 weeks prior to clinical evaluation.
	Use of Tetra-Hydro-Cannabinoid (THC) / cannabinoid containing substances is allowed if their use does not constitute abuse per local regulations and/or local medical practice.	Will be allowed if, in the opinion of the investigator, use does not represent an exclusionary condition, does not constitute abuse, does not affect cognition AND provided participants are currently treated with a stable regimen for at least 12 weeks prior to randomization. If initiated during study, e.g. for mood stabilization or pain, maintain a stable regimen in the six weeks prior to clinical evaluation. Resting state fMRI need not be performed during MRI examinations unless taken as-needed. If taken as-needed, these must be withheld for 72 hours prior to cognitive assessments and/or fMRI (as applicable).

5.5.9 Discontinuation of investigational treatment

Participants may voluntarily discontinue the investigational treatment for any reason at any time. In case of permanent study treatment discontinuation, participants are encouraged to continue attending study visits and remain in the study. IRT should be notified of permanent treatment discontinuation so that no more drug resupplies are planned for this participant.

Participants who progress to MCI/dementia due to AD should continue on their assigned investigational treatment. The Investigator should discontinue the investigational treatment for a given participant if, overall, he/she believes that continuation would be detrimental to the participant's well-being.

Investigational treatment may also be discontinued at the individual or study level, following regular safety evaluations or futility analysis review by the DMC.

The following circumstances will require stopping further investigational drug administration, in the respective participant, as assessed by the Investigator:

- In the case of progression to late-moderate or severe dementia or loss of capacity to consent, the participant should be discontinued from the study

- Withdrawal of study consent (participant wish) (Section 5.5.10)
- In the unlikely event of pregnancy
- Use of prohibited treatment leading to discontinuation as per Table 5-2 or meeting criteria for treatment discontinuation with restricted medications listed in Table 5-3, in the corresponding cohort
- Any other protocol deviation that results in a significant risk to the participant's safety
- Meeting the criteria for discontinuing the investigational treatment due to:
  - Clinically notable SAEs that require discontinuation of treatment (Section 13.1)
  - Other clinically notable findings including symptomatic ARIA-E or ARIA-H for Cohort I (Section 13.2)
  - Diagnosis of dementia not due to AD after confirmation of diagnosis by the Progression Adjudication Committee (PAC)
  - Clinically significant results of safety assessments deemed to be related to investigational drug that might put the participant at risk, including, but not limited to: MRI, clinical chemistry, hematology, vital signs, ECG (Section 13.3, Section 13.4).

In addition, investigational treatment should be suspended for participants when:

- Study partner is not available for a period of more than 3 months. When available again or a replacement study partner is identified, study treatment can be resumed
- They are taking medications listed in Table 5-2 for an acute condition

The appropriate personnel from the site and the Sponsor will assess whether study/investigational treatment should be discontinued for any participant whose treatment code has been broken inadvertently for any reason.

Participants who discontinue the investigational treatment should NOT automatically be considered withdrawn from the study unless there is explicit withdrawal of study consent from the study. They can continue attending study visits according to protocol assessments as planned in Table 6-2 to 6-4. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letters) should be made to contact them as specified in Section 5.5.11.

For participants who discontinue study injections in Cohort I for any reason, Extended SAE collection for safety monitoring is required to continue per protocol until a minimum of one year has elapsed since the last injection. If the participant does not attend the scheduled visits, quarterly telephone calls to detect SAEs will be placed to monitor safety until 12 months after the last injection has elapsed (see Section 6.2).

This strategy will allow monitoring safety in the participants in the initial phase of induction of the immune response in the first year of treatment, as well as over the 12 months after their last injection where antibody titers are expected to decline towards Lower limit of quantification in a large proportion of participants.

Participants enrolled in Cohort II (CNP520 or placebo) should be followed for 3 months (approximately 12 weeks) after their last intake of investigational treatment (once it is determined as a permanent study drug discontinuation) or PPW visit performed at which time they will perform the Follow-up visit assessment (EoS).

The Investigator must also contact the IRT to register the participant's discontinuation from investigational treatment, and also register the visits with no treatment dispensed until PPW/Treatment Epoch Completion (TEC) and EoS.

Re-randomization due to early termination of either cohort

Participants who discontinued the investigational treatment will not be eligible for renewed access to investigational treatment, unless the cohort they were originally randomized to is terminated early, in which case they may be eligible to be randomly reassigned and treated in the other cohort. This may apply specifically in case CAD106 meets the futility criteria after the CNS activity futility analysis. However, consideration for lowering the CNP520 dose will be given before terminating Cohort II; this decision will be made with all available data for CNP520 and in agreement with the DMC.

Re-randomization may also occur after the recruitment in a given cohort is complete, following an appropriate washout period:

- Cohort I: for CAD106, Aβ-specific antibody titers should be below serological responder threshold (Aβ-specific IgG titers ≥26.8 units)
  - Titers should be drawn every 3 months (i.e. at the study visits as the participants are encouraged to continue with the assessment schedule) for those participants that desire to be considered for re-randomization to Cohort II.
  - Participants who choose not to be considered for re-randomization, will have end of treatment date confirmed when titers are below threshold, unless they prematurely discontinue.

  or
- Cohort II: for CNP520, last dose should have been administered at least 30 days or 5 half-lives ago, whichever is longest.

If there are specific safety eligibility criteria for the ongoing cohort, participants will need to be rescreened and meet the criteria to be eligible for the ongoing cohort (beside age>75 will be waived). Following random reassignment, in the case that recruitment for the cohort has already been met, participants will receive study drug for the remaining duration that the treatment epoch is ongoing, (i.e. treatment duration may be less than 5 years for some re-randomized participants). Data handling from these participants will be described in detail in a protocol amendment that would be required in this situation (see details in Section 5.5.14).

5.5.10 Withdrawal of study consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a participant:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the participant's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

5.5.11 Loss to follow-up

For participants with unclear status because they fail to appear for study visits without stating an intention to withdraw, the Investigator should show "due diligence" by contacting the participant, study partner, family, or family physician, as agreed in the informed consent, and by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be formally considered lost to follow-up until the time for his/her scheduled EoS visit has elapsed.

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to ensure participant safety. Most often, investigational treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the site monitor for the site and the Global Trial Lead that the code has been broken.

It is the Investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The Investigator will inform the participants how to contact his/her backup in cases of emergency when he/she is unavailable. The Investigator will provide the protocol number, investigational treatment name if available, participant's number, and instructions for contacting the Sponsor (or any entity to which it has delegated responsibility for emergency code breaks) to the participants in case an emergency treatment code break is required at a time when the Investigator and backup are unavailable.

5.5.13 Study completion and post-study treatment

A participant will be considered a completer when he/she has completed all visits up to the Month 60 scheduled visit, either on/off treatment, including follow-up visits where required. The study will be considered completed when both the following conditions are met:

1. All individual participants have completed their month 60 scheduled visit
2. Target number of events has been reached in both cohorts

Upon study completion (assuming futility for one or both investigational drugs was not met), participants may have the opportunity to enter an extension under a separate study, if eligible. All SAEs, deemed suspected to study medication or not, which are reported during the Extended SAE collection for Cohort I will be collected in the Novartis safety database but will not be recorded in the clinical study data after the database lock (see reporting process in Section 7.2.2).

Assuming the target number of events was reached, the Treatment Epoch will complete at TEC visit within 3 months of when the last participant randomized and still receiving study treatment reaches month 60. This timing will be closely monitored and all sites will be notified in the preceding 6 months to schedule the TEC visit. All assessments described in the TEC column will be completed unless they were performed in the timeframe specified in footnotes 18 and 22 in Table 6-4.

5.5.14 Early study termination

Novartis may terminate the trial or Cohort for reasons related to the benefit risk assessment of treatment for participants in the study, or for regulatory or medical reasons (including slow enrolment) in consultation with the DMC. In the event that the study or either Cohort is terminated early, an amendment will be submitted for approval to Health Authorities and the IRBs/ECs. The amendment will include information on reasons for the early termination and the process to prematurely withdraw the participants (or, in the case of a terminated Cohort, a detailed benefit-risk assessment of the administration of CAD106 in patients previously treated with CNP520 and vice-versa and the process to re-randomize to the other Cohort). In general, the participant should be seen as soon as possible and assessed as a prematurely withdrawn participant from the study. The withdrawal process may include additional procedures to be followed, in order to ensure that adequate consideration is given to the protection of the participant's interests.

6 Visit schedule and assessments

6.1 Pre-screening Epoch and Genetic Disclosure Follow-up assessments

Individuals who present to the study site (with or without prior genetic information) will sign Informed consent #1B before Pre-screening assessments are performed. For those without knowledge of APOE genotype, all pre-disclosure clinical scales will be collected by study personnel, who are blinded to the participant's APOE genotype until disclosure. The study personnel will communicate results of the Pre-screening assessments to the counselor prior to disclosure. Only the genetic counselor, (or such equivalent according to local regulations (e.g. trained psychologist, study nurse or clinician) will have access to the individual genotype after the genetic counseling was conducted in order to proceed with disclosure of the participant's APOE genotype. The counselor will use the provided APOE risk information and talking points standardized across all sites. It is the responsibility of the investigator to confirm that the

participant continues to meet psychological readiness criteria before proceeding with genetic counseling and disclosure session.

Ideally, study participants should have APOE genotype information available (but not always known to them) at the time of Informed consent #1B. (This can be from local biobanks, local longitudinal studies, etc.) However, if the genotype is not yet available or needs to be repeated/confirmed, a buccal swab could be performed at the site after signing the Informed consent #1 (Part 1A). This prescreening genotyping will be performed at the Central laboratory, but genotyping confirmation must still be performed at Screening. A process of inviting a mix of HM and non-HM to return for counseling will be defined for each site and available for review by the local IRB/EC, as needed. This algorithm will determine the ratio of HM vs non-HM invited back to the study (refer to Appendix 2). In these cases, the buccal swab/genotyping would occur on a separate visit from the remaining pre-disclosure assessments in order to have sufficient time for Central laboratory to provide the genotype results.

To ensure some non-HMs are also invited to the disclosure visit, the identified site staff will receive the genotype results and identify the participants to be invited for the pre-disclosure assessments.

Only those participants who receive genetic disclosure/counseling will continue to perform post-disclosure assessments for up to 12 months (Genetic Disclosure Follow-up). Those participants who fail prescreening prior to the genetic disclosure do not need to continue to the Genetic Disclosure Follow-up. The HMs who are eligible and willing to continue in the double-blind study will enter the Screening Epoch upon signature of the Informed consent #2.

[redacted]

Safety follow-up for all participants who received genetic disclosure must still occur throughout the entire duration of the genetic disclosure follow-up epoch, regardless if they continue into the screening or treatment epochs (see Section 7.1). During these follow-up calls, site personnel will ask the participant about any unusual signs or symptoms. A follow-up visit with a study physician may be scheduled in such case, or if triggered by criteria described in Section 7.7. In the case of any notable safety related event stemming from the impact of disclosure, a corresponding adverse event must be recorded on the appropriate eCRF, including the relationship to the disclosure procedure.

For conditions identified/diagnosed during Prescreening and:

- are related to Genetic Disclosure: recorded as an AE;

- are unrelated to Genetic Disclosure: record as Medical History.

Refer also Section 6.3.2 and Table 7-1.

[redacted]

[redacted]

[redacted]

[redacted]

6.2 Screening Epoch and Treatment Epoch

Table 6-2 lists all of the Screening and Treatment Epoch assessments up to week 52. Table 6-3 and Table 6-4 list the Treatment Epoch assessments from week 65 to week 260 and Treatment Epoch and Follow-up assessments from week 273 to end of study respectively. An "x" indicates when the assessments are to be conducted. The Screening Epoch assessments will be performed over a maximum of 12 weeks duration. A missing or rescheduled assessment or combination of screening steps may be permitted provided that there is no impact on the assessment of eligibility criteria. See Section 3.1.2.1 for extended screening or re-screening criteria. Participants should be seen for all visits on the designated week or within a window of ±1 week for visits up to week 13 and ±4 weeks for visits beyond week 13. Exception to this window is for the additional assessments at Month 3 added in Amendment 5 under the USM; the RBANS and [redacted] can be performed up to 4 weeks prior to the Month 6 visit date. Scheduled study visits involving MRI, PET, and/or CSF sampling may require multiple visits spread over different days that should be scheduled within the ±4-week window. Participants should be seen as close as possible to the designated week. Every visit should be timed as per protocol from the baseline visit date, and not from the previous visit date. Missed or rescheduled visits or assessments should not lead to automatic discontinuation.

During screening, all participants are scheduled to perform Amyloid PET scans (Refer to Section 6.6.3.2 if amyloid PET is not available at screening). Voluntary participation in the biomarker assessments ([redacted], tau PET at subset of sites, year 2 and year 5 amyloid PET, CSF sampling, and blood sampling for biomarkers [redacted]) will require participants to consent specifically to these additional assessments.

Following early termination of CNP520 treatment in Cohort II per the 11-July-2019 USM notification, the mEoS Follow-up visits can be scheduled any time after receipt of the Follow-up #2 notification but no later than 15-Mar-2020, and may be converted to a phone call in case of logistical constraints.

Table 6-2 Screening and Treatment Epoch assessment schedule (Screening – Week 52)

Epoch	Screening	Treatment							
Visit Timepoint	**Screening[16]**	**Baseline (Day -1 to Day 1)**	**W7[17, 30]**	**W9[17]**	**W13 (Y1Q1)**	**W15[17]**	**W26 (Y1Q2)**	**W39 (Y1Q3)**	**W52 (Y1Q4)**
Visit Number	**201**	**301**	**302**	**303**	**304**	**305**	**306**	**307**	**308**
Sign study Informed consent #2	X[1]								
Inclusion /Exclusion criteria	X[12]	X[4]							
APOE Genotype confirmation (buccal swab)	X[28]								
Blood biomarkers [redacted] [2]					X[2]				
MCI/dementia diagnostic verification /Classification	X						X		X
Physical / Skin / Neurological exam[12]	X				X		X		X
ECG[26]	X				X[25]		X		X
Safety laboratory tests	X[6]				X		X		X
MRI (safety, volMRI, [redacted] [2, 9]) [14]	X						X		X
Amyloid PET[9]	X[3]								
Tau PET[29] (at subset of sites) / [redacted] [2, 9, 10]	X[3]								
Lumbar Puncture (CSF biomarkers and [redacted] [2, 11]	X[3]								
Blood biomarkers (Serum/Plasma) [2]		X[3]			X		X		X
[redacted]									
RBANS (APCC), Raven's (APCC), MMSE[7]	X[7]	X			RBANS only		X		X
CDR, ECog, [redacted] [7, 8]	X				[redacted]		X		X
[redacted]									
Cohort I (CAD106 or placebo)									
Vital signs[13]	X	X	X		X		X	X[12]	X
Drug Administration[27] / call IRT		X[5]	X		X		X	X	X
Reminder to fill Participant eDiary		X	X		X		X	X	X
Ant body response (serum, plasma)				X[19, 20]	X[19, 20]	X[19,20]	X	X[19, 20]	X
T-cell activation (N=50)		X		X					
Adverse events / eC-SSRS/Concomitant medications	X	X	X	X	X	X	X	X	X

Epoch	Screening	Treatment							
Visit Timepoint	Screening[16]	Baseline (Day -1 to Day 1)	W7[17, 30]	W9[17]	W13 (Y1Q1)	W15[17]	W26 (Y1Q2)	W39 (Y1Q3)	W52 (Y1Q4)
Visit Number	201	301	302	303	304	305	306	307	308
Cohort II (CNP520 or placebo)									
Vital signs	X	X			X		X	X	X
Drug Dispensing[27]/ Administration / call IRT		X[5]			X		X	X	X
[redacted]									
Adverse events / eC-SSRS/ Concomitant medications	X	X			X		X	X	X
Skin images for central dermatology review (also in case of skin-related event)	X								

Table 6-3 Treatment Epoch assessment schedule (Week 65 - Week 260)

Epoch	Treatment															
Visit Timepoint	Year 2				Year 3				Year 4				Year 5			
	W65 (Y2Q1)	W78 (Y2Q2)	W91 (Y2Q3)	W104 (Y2Q4)	W117 (Y3Q1)	W130 (Y3Q2)	W143 (Y3Q3)	W156 (Y3Q4)	W169 (Y4Q1)	W182 (Y4Q2)	W195 (Y4Q3)	W208 (Y4Q4)	W221 (Y5Q1)	W234 (Y5Q2)	W247 (Y5Q3)	W260 (Y5Q4)
Visit Number	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324
MCI/dementia diagnostic verification		X		X		X		X		X		X		X		X
Physical /Skin/ Neurological exam[12]		X		X		X		X		X		X		X		X
ECG[26]		X		X		X		X		X		X		X		X
Safety laboratory tests		X		X		X		X		X		X		X		X
MRI (safety, volMRI, [redacted], [9]) [14]				X				X				X				X
Amyloid PET[2]				X[2]												X[2]
Tau PET[29] (at subset of sites)[2]				X												X
[redacted]																
CSF biomarkers and [redacted]				X												X
Blood biomarkers (Serum/Plasma) [2]				X												X
[redacted]																

Epoch	Treatment															
Visit Timepoint	Year 2				Year 3				Year 4				Year 5			
	W65 (Y2Q1)	W78 (Y2Q2)	W91 (Y2Q3)	W104 (Y2Q4)	W117 (Y3Q1)	W130 (Y3Q2)	W143 (Y3Q3)	W156 (Y3Q4)	W169 (Y4Q1)	W182 (Y4Q2)	W195 (Y4Q3)	W208 (Y4Q4)	W221 (Y5Q1)	W234 (Y5Q2)	W247 (Y5Q3)	W260 (Y5Q4)
Visit Number	**309**	**310**	**311**	**312**	**313**	**314**	**315**	**316**	**317**	**318**	**319**	**320**	**321**	**322**	**323**	**324**
RBANS (APCC), Raven's (APCC), MMSE[7]		X		X		X		X		X		X		X		X
CDR, ECog, [redacted] [8]		X		X		X		X		X		X		X		X
[redacted]																
Cohort I (CAD106 or placebo)																
Vital signs[13]	X[12]	X	X[12]	X	X[12]	X	X[12]	X	X[12]	X	X[12]	X	X[12]	X	X[12]	X
Drug Administration[27] / call IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reminder to fill Participant eDiary				X				X				X				
Ant body response (serum, plasma)	X[19, 20]	X	X[19, 20]	X		X		X[19, 20]		X		X		X[19, 20]		X
Adverse events / eC-SSRS / Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cohort II (CNP520 or placebo)																
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Dispensing[27] / Administration/ call IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																
Adverse events / eC-SSRS/ Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 6-4 Treatment Epoch and Follow-up Epoch assessment schedule (Week 273 – End of Study)

Epoch	Treatment														
Visit Timepoint	Year 6				Year 7				Year 8						
	W273 (Y6Q1)	W286 (Y6Q2)	W299 (Y6Q3)	W312 (Y6Q4)	W325 (Y7Q1)	W338 (Y7Q2)	W351 (Y7Q3)	W364 (Y7Q4)	W377 (Y8Q1)	W390 (Y8Q2)	W403 (Y8Q3)	W416 (Y8Q4)	PPW[18]	TEC[22]	
Visit Number	**325**	**326**	**327**	**328**	**329**	**330**	**331**	**332**	**333**	**334**	**335**	**336**	**399**		
MCI/dementia diagnostic verification		X		X		X		X		X		X	X	X	

Epoch	Treatment														
Visit Timepoint	Year 6				Year 7				Year 8						
	W273 (Y6Q1)	W286 (Y6Q2)	W299 (Y6Q3)	W312 (Y6Q4)	W325 (Y7Q1)	W338 (Y7Q2)	W351 (Y7Q3)	W364 (Y7Q4)	W377 (Y8Q1)	W390 (Y8Q2)	W403 (Y8Q3)	W416 (Y8Q4)	PPW[18]	TEC[22]	
Visit Number	325	326	327	328	329	330	331	332	333	334	335	336	399		
Physical / Skin/ Neurological exam[12]		X		X		X		X		X		X	X	X	
ECG[26]		X		X		X		X		X		X	X	X	
Safety laboratory tests		X		X		X		X		X		X	X	X	
MRI (safety, volMRI, [redacted][2, 9]) [14]				X				X				X	X	X	
Amyloid PET													X[18]	X[22]	
Tau PET[29]													X[18]	X[22]	
CSF biomarkers[2]													X[18]	X[22]	
Blood biomarkers (Serum/Plasma)[23]													X[18]	X[22]	
[redacted]															
RBANS (APCC), Raven's (APCC), MMSE[7]		X		X		X		X		X		X	X	X	
CDR, ECog [redacted][, 8]		X		X		X		X		X		X	X	X	
[redacted]															
Cohort I (CAD106 or placebo)															
Vital signs[13]	X[12]	X	X[12]	X	X[12]	X	X[12]	X	X[12]	X	X[12]	X	X	X	
Drug Administration[27] / call IRT	X	X	X	X	X	X	X	X	X	X	X				
Reminder to fill Participant eDiary															
Ant body response (serum, plasma)		X[19, 20]		X		X		X		X		X	X	X	
Adverse events / eC-SSRS/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cohort II (CNP520 or placebo)															

Epoch	Treatment														
Visit Timepoint	Year 6				Year 7				Year 8						
	W273 (Y6Q1)	W286 (Y6Q2)	W299 (Y6Q3)	W312 (Y6Q4)	W325 (Y7Q1)	W338 (Y7Q2)	W351 (Y7Q3)	W364 (Y7Q4)	W377 (Y8Q1)	W390 (Y8Q2)	W403 (Y8Q3)	W416 (Y8Q4)	PPW[18]	TEC[22]	
Visit Number	325	326	327	328	329	330	331	332	333	334	335	336	399		
Vital signs	X	X		X		X		X		X		X	X	X	
Drug Dispensing[27] / Administration / call IRT	X	X	X	X	X	X	X	X	X	X	X	X[24]			
[redacted]															
Adverse events / eC-SSRS/ Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Cohort I (CAD106 or placebo)	Follow up[15]
Visit Name	EOS
Visit Numbers	401
MCI/dementia diagnostic verification	X
Physical / Skin/ Neurological exam[12]	X
ECG[26]	X
Safety laboratory tests	X
RBANS (APCC), Raven's (APCC), MMSE[7]	X
CDR, ECog, [redacted][7, 8]	X
[redacted]	
Vital signs[13]	X
Antibody response (serum, plasma)	X[19]
Adverse events / eC-SSRS/Concomitant medications	X[21]

Cohort II (CNP520 or placebo)	Follow up
Visit Name	mEOS[15]
Visit Numbers	401
MCI/dementia diagnostic verification	
Physical / Skin/ Neurological exam[12]	
ECG[26]	
Safety laboratory tests	
RBANS (APCC), Raven's (APCC), MMSE[7]	
CDR, ECog, [redacted][7, 8]	
[redacted]	
Body Weight	X (only if on-site visit)
[redacted][23]	
Adverse events / Concomitant medications	X
eC-SSRS	X (only if on-site visit)

TEC =Treatment Epoch completion; PPW= Premature Participant Withdrawal; APCC = API Preclinical composite cognitive; CDR = Clinical dementia rating; C-SSRS = Columbia Suicide Severity Rating Scale; ECog = Everyday Cognition scale; PRO = Patient reported outcome; [redacted]; MCI = Mild cognitive impairment; MedDRA = Medical Dictionary for Regulatory Activities; MFAS= Modified full analysis set; MMRM = Mixed model repeated measure; MMSE = Mini-Mental State Examination; MRI = Magnetic resonance imaging; [redacted]; PET = Positron emission tomography; RBAN =Repeatable Battery for the Assessment of Neuropsychological Status.

1. **Note: On treatment days, all assessments should be performed prior to dosing unless otherwise noted. Participants should be seen for all visits on the designated week or within a window of ±1 week for visits up to week 26 and ±4 weeks for visits beyond week 26.** Obtain informed consent prior to conducting any assessments. Informed Consent Forms must be signed by the participant and study partner.
2. Ensure participant has signed the required informed consent for voluntary participation for the PET scans (Year 2 and Year 5 Amyloid PET, tau PET (at subset of sites) [redacted], collection of CSF (exception: mandatory at screening if amyloid PET is not feasible) and blood for biomarkers and blood for DNA before performing these assessments. Although part of the screening period, eligibility is not dependent upon PET (amyloid, tau [redacted]) results. In locations where compliance with total radiation exposure limits could be of concern, voluntary tau PET scans are to be prioritized over voluntary FDG PET scans.
3. All PET scans, as well as biomarker collection (CSF and blood) should be performed after the participant is deemed eligible on the basis of all other screening assessments, including the MRI. Site should allow sufficient time to receive MRI safety interpretation prior to performing any PET scan or lumbar puncture.
4. Review study criteria to ensure that the participant still qualifies to participate in the study.
5. All baseline assessments must be completed before first administration dispensing of investigational treatment (Day 1).
6. Sample should be taken on the same day consent was obtained to ensure adequate time for testing and reporting of results. Safety laboratory tests at screening include urine drug test for eligibility and serology for HIV and Hepatitis B and C (verified as described in Section 6.5.4) and urine sample for analysis of creatinine, albumin and total protein and their respective and ratios. PT/INR also required for participants that consent to Lumbar Puncture.

7. Cognitive assessments should not be administered to the participant immediately after any potentially stressful procedures (e.g. blood draws, LP, imaging). Also, participants should not perform these assessments while fasting. For each participant, best efforts should be exerted to perform subsequent assessments at the same time of day as the baseline /screening assessments. MMSE at V201 may be skipped if the V101 MMSE was administered by a certified rater and in the previous 3 months (refer to Section 3.1.2.1)
8. Scale requires presence from the study partner: ECog is self-reported by the Informant, and CDR needs to be on-site for audiorecording required for central review. However, [redacted] only can be collected over the phone.
9. [redacted], tau PET and amyloid-PET should be performed according to instructions from the Imaging Manual. For each participant, the same PET tracer should be used at all amyloid PET scans, and best efforts should be exerted to perform subsequent PET scans at the same time of day as screening scan (note that results of the tau PET is not required for eligibility. In exceptional cases related to documented scheduling issues, tau PET scan can be performed within a maximum 4 weeks after the randomization date.). In case sedation is required for Amyloid PET scans, allow for 72 hours before cognitive assessments. No sedative are allowed in the 72 hours prior to [redacted]. If amyloid PET is not feasible, then CSF amyloid assessment is mandatory at Screening (Refer also to Footnote #2.)

[redacted].

11. LP should be performed preferably in the morning and at the same time of the day before dosing. A light breakfast is allowed and should be taken 2 hours prior to LP, however, fasting is not prohibited. Participants will be required to stay in the clinic for approximately 2-hour after the LP for safety follow-up. For each participant, best efforts should be exerted to perform subsequent LP's at the same time of day as the baseline LP
12. Assessment to be recorded on source documentation only and will not be entered into the eCRF. In the case of findings): record corresponding adverse event. In case of dermatological findings during skin examination for Cohort II: take a picture for central dermatological reading; if participant is at home, arrange for site visit and perform unscheduled skin examination.
13. Cohort I: During visits where investigational treatment is administered on site, vital signs should be taken prior to dosing, and then 30 minutes post-dose (±5 minutes) and one hour post-dose (±10 minutes).
14. Follow-up MRI to be scheduled 2 weeks before each respective visit, to ensure that safety assessments from the central reader are available before the scheduled drug administration. In case sedation is required allow for 72 hours before cognitive assessments.
15. End of Study Follow-up visits are to be scheduled 26 weeks after last injection of CAD106 for Cohort I and for Cohort II : within 12 weeks after mTEC visit. Can be converted to phone call in case of logistical constraints.
16. The Screening Epoch assessments will be performed over a maximum of 12 weeks
17. Visit is only applicable to Cohort I (CAD 106 or matching placebo). These visits should always be as close as possible from 2 weeks (14 days) from the actual day of last injection. Do not calculate back in reference to baseline.
18. Participants who withdraw prematurely during the course of the trial will be asked to come to the site for a PPW visit. The same procedures are expected at PPW as for the Treatment Epoch Completion visit (TEC). For Cohort I only: Conditional assessments to be repeated upon PPW/TEC: MRI and blood AD biomarkers if last one were more than 6 months ago, tau PET, amyloid PET scans and Lumbar Puncture if last one was more than 18 months ago with in addition, PET scans, CSF and blood for biomarkers to be performed on participants who consented at screening if PPW occurs before year 5 and at least 18 months after previous biomarker assessments (e.g. 18 months after baseline or year 2). For Cohort I, this visit should always be scheduled at least 3 months after last injection of study medication.

[redacted]

21. For Cohort I: Extended SAE collection for 1 year after the last study visit. Safety telephone call to be placed by the site to the participant, his caregiver and/or his general practitioner at 3, 6, 9 and 12 months after the last study visit (EoS or PPW). Any SAE (whether suspected to be related to study medication, or not) will be recorded (see Section 7.2.2).
22. Treatment Epoch Completion (TEC) after early study termination, all ongoing participants will come to their next scheduled visit to perform the TEC visit. In Cohort II, the tau PET and Amyloid PET scans are cancelled at the mTEC.
23. In Cohort II, Aβ1-40 in plasma will be assessed at every [redacted] time-point.
24. In Cohort II, at Visit 226 (Week 416): last dose administered; no study medication will be dispensed.

25. ECG at Visit 303 (week 13) is only applicable to Cohort II.

26. All ECGs to be taken in triplicate ECGs. During the treatment period, ECGs to be taken approximately 2.5 hours after treatment administration at the site (see Section 6.5.5)

27. Last drug administration (Cohort I) or dispensing (Cohort II) will be at the visit which is 3 months prior to the planned Treatment Epoch Completion visit.

28. Screening genotyping can be waived if the participant was genotyped under ICF#1 Part1A and using a generation program Covance buccal swab kit.

29. Tau PET not performed in Germany

30. Interim check in at Week 7 to assess compliance,

6.3 Screen failures, demographics/other Baseline characteristics

6.3.1 Information to be collected on screening failures

All participants who have signed Informed Consent #2 at entry in the Screening Epoch but screen failed and are not randomized, will have the study completion page for the previous Epoch, demographics, screening inclusion and exclusion criteria, and SAE data collected. AEs related to the genetic disclosure will be captured in the eCRF. AEs that are not SAEs and not related to the genetic disclosure will be followed by the Investigator and collected only in the source data.

In addition, results from safety MRI, volumetric MRI, and Amyloid PET standardized uptake ratio (SUVR) obtained during the Screening period will be collected also for participants who screen fail when available.

6.3.2 Demographics/other Baseline characteristics

Participant demographic and Baseline characteristic data to be collected on all participants include: date of birth (year only, where applicable), sex, race, ethnicity, referral source, family history of AD, and years of education.

Relevant medical history/current medical conditions present before signing the Informed consent #2 will be recorded, preferably as diagnoses instead of symptoms, when possible. Refer also to Table 7-1. If the condition was identified/diagnosed during Screening (after ICF#2), this should be recorded as an AE (i.e. does not have to be related to Genetic Disclosure).

In addition, all scheduled assessments during the Pre-screening and the Screening on-site visits will be collected and used as Baseline reference vs. post-randomization measures. In case an assessment is repeated, the latest one will be used as the Baseline.

Investigators will have the discretion to record abnormal examination findings on the medical history eCRF that, according to their judgment, the examination abnormality occurred prior to the Informed consent #2 signature.

The study partner characteristics will be collected on the Virgil® tablet. It will capture the study partner's relationship with the participant and frequency of contact with the participant. Temporary unavailability of or changes in study partner will also be recorded on the eCRF.

6.3.3 Assessment of unimpaired cognition at Screening: Diagnostic Verification Form

Criteria for diagnosis at screening will be assessed by the investigator as described in Section 6.4.1 and will complete the diagnostic verification form (DVF) on the Virgil® tablet. The DVF must be completed as specified in Table 6-2. It is recommended to complete the DVF one week after CDR and RBANS have been completed to ensure centralized review by the cognitive vendor has occurred, when applicable. The feedback from centralized review must be addressed and scores adjusted accordingly by the respective raters and before the PI or his/her delegate completes the DVF (note DVF should not be completed by the CDR rater).

Diagnostic has to be verified as unimpaired cognition before invasive procedures such as MRI or later amyloid assessments such as PET/LP.

6.3.4 Other screening considerations

Scheduling of the screening activities should be closely monitored when approaching the completion of recruitment, to ensure the participant can still be randomized before enrollment is completed.

A missing or rescheduled assessment or combination of screening steps may be permitted if not impacting the 12-week timeline for assessment of eligibility criteria.

Participants who fail eligibility during the screening process for a temporary condition (e.g. physical, concomitant medications, etc.) will be allowed to be re-screened at a later stage. When all inclusion and exclusion criteria will have to be re-verified a new participant number will be assigned. A participant initially excluded for a condition no longer exclusionary upon a protocol amendment can also be re-screened.

6.3.5 Screening extension beyond 12 weeks

The total duration of 12 weeks for screening assessments may be extended only if the following conditions are met:

- The participant has not failed any eligibility criteria (if so, see below for potential re-screening in case of temporary conditions).
- Any screening (including Baseline) assessment supporting eligibility criteria must be collected within 12 weeks before the date of randomization. Assessments that are collected again during screening/baseline per Table 6-2, can be used to verify eligibility in the 12-week timeframe, with an exception for MRI that can support eligibility if collected within 16 weeks before randomization. Screening results from amyloid PET scan/lumbar puncture (performed under this study) to verify brain amyloid levels are valid without any time limitation (i.e. 12 week period) and do not need to be repeated before randomization. This is relevant in the event of logistical issues related to scheduling of imaging (MRI, PET scans) or lumbar puncture.
- For cognitive scales, CDR and RBANS are required for eligibility. While RBANS is repeated at both screening and baseline, CDR is only collected once at screening and must be collected within the 12 weeks prior to randomization.
- In such case, the corresponding repeat CDR will be collected in Virgil ideally 5 days before Randomization to allow for centralized review (if applicable). On the same day, the cognitive scales scheduled for Baseline should be administered (including RBANS Form A to verify the DMI score for inclusion). This approach leads to a split of assessments from Baseline on 2 different calendar days. Before randomization, the Diagnostic Verification Form (DVF) must be updated with the corresponding CDR and RBANS Delayed Memory Index (DMI) scores to verify eligibility.

Also see Section 6.4.2 for APCC requirements during Screening.

6.4 Efficacy

All scales listed and described in this section are administered directly on Virgil tablet used as electronic Source Document. Various clinical and participant/informant reported scales will assess changes in cognition, functional status, and neuropsychiatric symptoms: RBANS, Raven's Progressive Matrices, MMSE, CDR, ECog, [redacted], [redacted]. They will be performed prior to randomization, with the last assessment being used as the baseline reference score.

Cognitive testing must be administered by a clinician/rater certified by the Rater Training Program of the dedicated Cognition vendor. The selected raters will complete a pre-qualification survey. Criteria for granting "pre-qualification" status is based on a rater's education, experience with the population and their prior experience with each scale. A rater's final qualification will require training on the Virgil® system, and specific training for the selected scale.

When possible, the same evaluator should administer a given test across all visits for a given participant. The initials of the evaluator will be collected for all primary efficacy scales on the Virgil® tablet. The CDR rater should be different from the evaluator administering the other clinical scales listed above. The CDR rater for a given participant will have no access to either the cognitive or other test results (i.e. using a separate user ID on the Virgil® tablet). The physician completing the diagnostic evaluation form should not have rated the CDR at that visit.

If not available from previous 3 months documentation, the initial MMSE at the first Pre-Screening visit may be administered by a non-certified rater using a paper version of the MMSE (not transcribed to Virgil in such case).

Instructions as to how to perform these assessments and their optimal sequence will be provided in the rating scales administration information from the Cognition vendor. The scales used for the primary and key secondary endpoints (i.e., MMSE, RBANS, CDR) will undergo a central review based on an algorithm implemented by the Cognition vendor. The central review is intended to ensure enrollment of participants who fit protocol parameters, to maintain high level of accuracy and reliability of endpoints by review of divergent scoring across sites or between raters. All data from the clinical scales will be recorded on the Virgil® tablet, collected in the database from the Cognition vendor and transferred to Novartis, except for the audio recording that will not be transferred to Novartis.

Completed questionnaires will be reviewed and examined by the investigator for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator should review not only the responses to the questions in the questionnaires but also any unsolicited comments from the participant. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

6.4.1 MCI due to AD or dementia due to AD (MCI/dementia) criteria assessment

The core clinical diagnostic criteria proposed by the National Institute on Aging - Alzheimer's Association Working Group will be used for diagnosis of MCI (Albert et al 2011) or dementia (McKhann et al 2011). Application of these criteria requires the judgment of an experienced clinician, taking into account clinical, cognitive, and functional criteria that define these syndromes.

Criteria for MCI due to AD will be defined by the following:

1. Clinical and cognitive criteria
   a. Concern regarding a change in cognition
   b. Impairment in one or more cognitive domains
   c. Preservation of independence in functional abilities
   d. Not demented
2. Examine etiology of MCI consistent with AD pathophysiological process:
   a. Rule out vascular, traumatic, medical causes of cognitive decline, where possible
   b. Provide evidence of longitudinal decline in cognition, when feasible

The MCI diagnosis is expected to be the first diagnosis for the majority of the participants. With the six month visit intervals for cognitive assessments and potentially rapid progression in APOE4 HMs, it is possible that some participants may be diagnosed directly with dementia.

The differentiation of dementia from MCI will rest on the determination of whether or not there is significant interference in the ability to function at work or perform usual daily activities; based on clinical judgment of the individual circumstances of the participant, the review of relevant scales using both participant and informant component scores, and the description of daily activities of the participant obtained from the participant and from the study partner.

Criteria for diagnosis will be assessed by the Investigator based on his or her overall clinical judgment and supported by review of measures of cognitive function (RBANS, MMSE), global measure of function/cognition (CDR-SOB), measures of daily function and measure of Subjective/observer memory concerns (ECog – both informant [study partner] and participant versions), Baseline data and other assessments (e.g. [redacted], MRI or other safety tests as needed).

In addition to the diagnosis made by the Investigator, an independent Progression Adjudication Committee (PAC) will review all MCI/dementia diagnoses. The PAC will be managed by the Cognition vendor. A description of the adjudication process, role and function of the PAC members are briefly presented in Section 8.5 and will be described in details in a specific charter.

The adjudication process will be triggered by:

- A change in diagnostic status as captured on the Diagnostic Classification Form on the Virgil® tablet; or
- Any increase from baseline on the global CDR score until the diagnosis of dementia has been established.

The final diagnosis will require confirmation at the next protocol-specified cognitive assessment visit. Any participant identified as having progressed from normal to MCI due to AD or dementia due to AD or any increase on the global CDR score, will have data from both the current visit and the next protocol-specified visit sent for PAC review/adjudication.

If there is a complaint of unexpected cognitive or functional deterioration reported by the participant or study partner between 6-monthly cognitive assessment visits, an unscheduled visit will be performed. The Investigator will evaluate non-AD related potential causes of cognitive decline as appropriate (e.g. Physical/Neurological evaluation, labs, ECG, MRI, including unscheduled assessments if needed). Full cognitive assessments and initiation of the adjudication process will be conducted at the next scheduled visit. A minimum window of 4 months from the previous cognitive assessment visit would be required to still fit in the allowed +/- 4 weeks window between 2 visits.

If there is any reason to suspect a non-AD etiology for the participant's change in diagnostic classification, an unscheduled visit may be performed for evaluation of possible non-AD related causes of cognitive decline as appropriate.

A diagnosis of MCI due to AD or Dementia due to AD made at any time other than a 6-monthly cognitive assessment visit will not trigger the adjudication process. The process will be triggered at the next cognitive assessment visit with the investigator updates the diagnostic verification form or the results of cognitive assessments support the diagnosis as described above.

Once the adjudication process is triggered, the change in diagnostic classification must be confirmed at the next 6-monthly cognitive assessment visit. Once confirmed, the date of the initial adjudicated diagnosis (not the clinical diagnosis in the event it is made between cognitive assessment visits) will be used to establish the date for the time to event analysis.

If the PAC and the Investigator do not agree on diagnosis, the PAC diagnosis will be used for analysis purposes.

The PAC diagnoses will be communicated to the sites. The date and final diagnosis after the adjudication process is completed will be captured in the database and used for analysis.

No submitted cases will be re-adjudicated unless additional information provided by the trial site has a potential impact on the adjudication of the case.

6.4.2 API Preclinical Composite Cognitive (APCC) battery

The APCC score will be derived from the 7 following tests performed as part of the cognitive scales administered during the study (see Table 6-2, Table 6-3 and Table 6-4, if applicable)

- MMSE:
  Orientation to Time
  Orientation to Place
- RBANS:
  - List Recall
  - Story Recall
  - Coding

- Line Orientation

- Raven's Progressive Matrices – subset

All scales used to derive the APCC test score (RBANS, MMSE and Raven's) will be administered twice during the Screening Epoch: first to assess inclusion (Screening) and a second time prior to randomization (Baseline pre-dose). A minimum interval of 4 weeks should be respected between two administrations of the APCC scales or CDR.

Of note: In case a repeat assessment of to confirm unimpaired cognition (Refer to Section 6.1).

Of note: In case a repeat assessment of CDR and RBANS is required during screening to confirm unimpaired cognition (see Section 3.1.2.1), CDR and RBANS can be repeated 5 days before the scheduled Randomization (using the Baseline scales that include RBANS Form A, and the other APCC scales).

Refer to Appendix 4 for details on assessment from study partner and conditions of administration/presence at visits.

6.4.3 Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS (Randolph 1998) is a clinical tool that was specifically designed for both diagnostic purposes and for tracking change in neurocognitive status over time. One of the key design goals of the battery is to detect and characterize the earliest neurocognitive changes associated with the earliest stages of dementia. The RBANS has no floor or ceiling effects in either cognitive normal older adults or in patients with amnestic MCI, despite the fact that these two groups have mean scores on the RBANS nearly two standard deviations apart (Karantzoulis et al 2013). RBANS scores have been reported to be correlated with cerebral amyloid in both cognitive normal individuals (Duff et al 2013) and in patients with MCI due to AD (Mukai et al 2015).

The RBANS is relatively brief (< 25 minutes) to administer, has four equivalent alternate forms, and 25 linguistically- and culturally-validated translations. The RBANS generates age-adjusted index scores for five neurocognitive domains which are used to calculate a Total Scale Index score.

The RBANS is comprised of the following domains, with associated subtests used for Index scores:

- Immediate Memory – List Learning and Story Memory (IMI)
- Visuospatial/Constructional – Figure Copy and Line Orientation
- Language – Picture Naming and Semantic Fluency
- Attention – Digit Span and Coding
- Delayed Memory – List Recognition and Sum of (List Recall, , Story Recall, and Figure Recall; DMI)

The RBANS Delayed Memory index score is used as an inclusion criterion, together with the CDR global score, to ensure selection of participants with unimpaired cognition at screening. With a normal mean score of 100 and standard deviation of 15, the 85 and 70 cut-offs for inclusion correspond to 1SD and 2SD below the normal mean, respectively. Participants who score between 85 and 70 will be considered suitable for the study only if their CDR global score is 0, confirming the absence of any clinically-detectable memory decline.

RBANS comes in four different versions labeled A, B, C, D. The version order for use at each visit will be defined in the Virgil Tablet. Generally, it follow a sequential pattern: Form B, A, C, D, B, A, C, D and so on. See Table 6-5 for which version form should be used at each visit. The exception for this pattern is the Month 3 assessment, which is introduced only with v05 of the protocol and will use Form D.

Table 6-5 RBANS version by visit

Visit	RBANS version
Screening (and repeat screening, if needed)	Form B
Baseline	Form A
Month 3*	Form D*
Month 6	Form C
Month 12	Form D
Subsequent visits follow sequential pattern	Form B, Form A, Form C, Form D, Form B, etc

*Month 3 assessment uses form D, which deviates from the sequential pattern, as the assessment for this visit was introduced with v05 of the protocol.

6.4.4 Raven's Progressive Matrices

Raven's Progressive Matrices (Raven et al 1992, Raven et al 1998, Raven et al 2000) is a non-verbal, multiple choice measure of general ability and reasoning using a visual modality. It was designed to be culturally nonbiased, as neither language nor academic skills are required to answer items successfully. The test requires conceptualization of spatial design and numerical relationships with varying levels of difficulty. For each item a participant is asked to identify the missing component to complete a pattern.

Although all components of the Raven's Progressive Matrices Set A and Set B will be assessed, in order to calculate the APCC test score, only a subset of items from Sets A and B will be used (items A2, A4, A8, B1-B6), with a total score from 0 to 9.

[redacted]

6.4.6 Mini Mental State Examination (MMSE)

The MMSE is a brief, practical test to examine cognitive status (Folstein et al 1975). It evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and the ability to create a sentence and copy two intersecting pentagons.

The test consists of five Sections (orientation, registration, attention, recall, and language) with a total score ranging from 0 to 30. A higher score indicates better cognitive function. The 5 sub scores as well as the total score will be recorded.

Although all components of the MMSE will be assessed, for calculation of the APCC test score, only the Orientation to Time and Orientation to Place scores from the MMSE (each of which ranges from 0 to 5) will be used.

The initial MMSE at first screening visit may be skipped if documentation of a MMSE performed in previous 3 months exists. When administered in the first screening visit, it can be done on paper and not uploaded in Virgil if rated by a non-certified rater.

All other screening, baseline and post-baseline tests will be administered and collected using the Virgil® tablet, except for the MMSE drawing and sentence pages that will be paper based. Pictures of the drawing and sentence will be taken and uploaded electronically to the tablet.

6.4.7 Clinical Dementia Rating Scale - Sum of Boxes (CDR-SOB)

The CDR is a global measure that evaluates cognition and functional performance and is widely used in clinical research in AD (Morris 1993). The scale assesses six domains: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. Each domain is assigned a score, which are summed to obtain the sum of boxes (SOB) score.

The necessary information for assessment is obtained through a semi-structured interview of the participant and a reliable informant or collateral source (i.e. study partner). Descriptive anchors are provided for each score that guide the clinician in making appropriate ratings based on interview data and clinical judgment, in order to evaluate the staging severity of the dementia.

The global CDR scores and CDR-SOB scores will be collected. Global scores range from 0 to 3, with greater scores indicating greater disease severity. CDR-SOB scores range from 0 to 18 with greater scores indicating greater disease severity.

Clinician judgment of MCI or dementia (see Section 6.4.1) and/or a change in the global CDR score will trigger the adjudication process.

6.4.8 Everyday Cognition Scale (ECog)

The 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 (Farias et al 2008).

The questionnaire is a self-reported measure completed by both participant and study partner (informant).

Within each domain, ability to perform a specific task is rated on a six-point scale ranging from: 1) no difficulty, 2) mild difficulty, 3) moderate difficulty, 4) severe difficulty, or 5) unable to do.

The total score for the 39 items ranges from 39 to 195, with greater scores indicating worse daily function. The study will include a modified version of the ECog scale to measure a static state (not a change), assessed at regular, 6 month intervals to minimize recall bias.

[redacted]

6.4.12 Appropriateness of efficacy assessments

Postponing the diagnosis of MCI and/or dementia represents an important clinical outcome with high face validity. The core clinical diagnostic criteria proposed by the National Institute on Aging - Alzheimer's Association working group will be used (Albert et al 2011, McKhann et al 2011) and will be assessed and operationalized as described in Section 6.4.9.

Preclinical cognitive decline due to AD is expected to be detectable with the proposed APCC test score. Decline on the APCC test score will provide a continuous measure of cognitive decline associated with progression to the clinical stages of MCI and/or dementia due to AD.

The APCC battery includes well-established, validated cognitive assessments that are expected to begin to decline prior to the onset of MCI or dementia due to AD and continue to decline during the clinical course of the disease. The composite is constructed from validated cognitive assessments across multiple cognitive domains (e.g., episodic memory, executive function, visual-spatial function) that reflect the spectrum of cognitive deficits of AD. Decline in these cognitive domains is associated with and predictive of functional decline in AD (Farias et al 2003). In addition, many of the cognitive domains included in the composite measure have been shown to correspond directly to participant and caregiver concerns in early disease (v et al 2014). The derivation of the proposed APCC battery and its resulting test score is described Section 9.4.

Secondary endpoints are chosen to evaluate the effects of the two selected investigational drugs on other clinical aspects of the disease and underlying AD pathology through appropriate soluble and imaging biomarkers.

The ECog combines subjective report of both cognitive and instrumental difficulties of daily living obtained from participants, as well as from a study partner who knows the participant well, which makes it especially appealing for assessing individuals with preclinical AD and those who expected to progress to MCI.

The long term impact of genetic disclosure is captured using various scales described in Section 6.1 aimed at assessing psychological impact.

6.5 Safety and tolerability

The current protocol describes general safety and tolerability assessments for both study investigational drugs (Cohort I: CAD106 and Cohort II: CNP520).

Clinically notable test findings are defined in Appendix 1. Only clinically significant abnormalities should be reported on the eCRF AE page for any of the assessments listed below.

6.5.1 Physical (including skin) and neurological examination

Physical examinations will be performed by a qualified clinician. They will include an examination of general appearance, skin (and skin reactions), neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes and extremities and vascular.

Neurological examinations (in particular, potential signs of adverse immune reaction for CAD106/Cohort I (Refer to Section 5.5.6)) will be performed by a qualified clinician. It will include mental status, cranial nerve function, function, motor function (tone, strength and reflexes), sensory function (small fiber, large fiber and cortical), coordination (cerebellar function) and balance/gait.

Information about both, the physical (including skin) and the neurological examinations, must be present in the source documentation at the study site. All significant findings which meet the definition of an AE must be recorded on the Adverse Event eCRF page

[redacted]

6.5.2 Vital signs

Vital signs include blood pressure, pulse, and temperature measurements. Systolic and diastolic blood pressure and radial pulse rate will be assessed after the participant has rested in the sitting position for at least 3 minutes. For Cohort I (CAD106 or placebo) participants on injection days, vital signs will be measured pre-dose, and at 30 and 60 minutes post-dose.

The vital signs data will be recorded on the corresponding eCRF pages as defined in Section 6.2.

Clinically notable vital signs are defined in Section 13.3.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at Screening. In addition, weight will be measured at all visits where vital signs are measured. See Section 13.3 Appendix 1.3 for definition of clinically notable changes.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples, and reporting of results by the central laboratory are provided to Investigators in the Laboratory Manual.

Clinically notable laboratory findings are defined in Section 13. Only clinically significant lab abnormalities should be reported on the eCRF AE page.

Screening lab tests

In addition to the regular laboratory tests described below, the following tests will be performed at Screening:

- A confirmatory buccal swab for APOE genotyping (note: this may be a repeat test if already performed during pre-screening). The samples will be analyzed to confirm APOE genotype and will also be stored for re-analysis with different assays / methods across all participants once the recruitment is completed.
- a urine drug screen for confirmation of eligibility and may be repeated once for the purpose of inclusion of participants who initially test positive but are not suspect of having engaged in drug abuse / use of illicit substances.
- A urine sample for analysis of creatinine, total albumin, total protein and their respective ratios
- A serology screening to test for Lyme disease (*boreliosis*) and Hepatitis B and C including reflex confirmation in case of positive IgG results (please refer to the available

Investigator Guide for interpretation), syphilis and HIV should be performed if not available from the past 12 months as is required to confirm eligibility criteria.

- In addition for participants consenting to the lumbar puncture procedure, prothrombin time international normalized ratio (PT/INR) will be measured for assessment of coagulation at screening and results required prior to the procedure.

Hematology

A standard hematology panel with differential counts will be performed. Hemoglobin (Hb), hematocrit, red blood cell count, platelet count, and white blood cell count with differential count as well as prothrombin time international normalized ratio (PT/INR) will be measured. In case treatment with a DOA is initiated during the study in a participant of Cohort I, additional laboratory testing to assess coagulation may be performed as required by the investigator.

Clinical chemistry

A standard blood chemistry panel will be performed: Albumin, total protein, alkaline phosphatase, total bilirubin, calcium, chloride, sodium, potassium, magnesium, inorganic phosphorus, bicarbonate, cholesterol (total / LDL / HDL), triglycerides, creatinine, creatine phosphokinase (CPK), gamma-glutamyl transferase (γ-GT), lactate dehydrogenase (LDH), lipase, α-amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glycated hemoglobin (HbA1c), blood urea nitrogen (BUN), uric acid C-reactive protein (CRP), thyroid stimulating hormone (TSH), Vitamin B12 and folate will be measured.

The creatinine clearance will be estimated from serum creatinine concentrations using the Cockroft-Gault formula.

The results should be available and reviewed before the MRI scans if gadolinium injection is required due to findings on the previous MRI scans.

Urinalysis

Dipstick measurements for specific gravity, protein, glucose, and blood will be performed at the site. In case of clinically significant abnormality, a urine sample will be sent to the central lab for analysis of the same parameters and in addition, creatinine, total albumin, albumin/creatinine ratio, white blood cells (WBC) and red blood cells (RBC) sediments.

6.5.4.1 CSF cell count

For participants in whom a CNS-related safety concern arises, an aliquot of CSF will be used for local measurement of CSF cell counts. Cell counts will include erythrocytes (as an indicator of blood contamination) and total white blood cells. The location of the facility where the lumbar puncture procedure is done must take into account that samples can only be analyzed if processed within two hours at the local laboratory facility. The data will be entered on the corresponding eCRF pages.

6.5.5 Electrocardiogram (ECG)

ECGs will be centrally evaluated. Full details of all procedures relating to the ECG collection and reporting will be contained in the technical manual which is provided to the site by the centralized ECG vendor.

Twelve-lead standard ECGs will be recorded in triplicate (one minute apart) after participants have been resting in the supine position for at least 10 minutes. The ECGs should be scheduled approximately 2.5 hours post CNP520 drug administration (median T_{max} for CNP520 at steady state) on site (Refer also to Section 5.5.4). The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Electrocardiograms will be obtained as designated in Table 6-2, Table 6-3 and Table 6-4, if applicable.

The ECGs readings will be sent automatically to the centralized ECG vendor. Findings at baseline, considered as clinically significant and meeting alert values, in the opinion of the Investigator, must be discussed with the Medical Monitor before administration of investigational treatment.

Clinically significant abnormalities should be recorded on the relevant Section of the Medical History/Current Medical Conditions/AE eCRF page as appropriate.

6.5.6 Safety brain MRI scans

Safety MRI will include the following sequences:

- 3D T1-weighted, structural T1 MPRAGE/IR-FSPGR/TFE (with acceleration) (also used for volumetric MRI, see Section 6.6.3.1 and replicated within the same session)
- Axial FLAIR (for general ascertainment of brain abnormalities including ARIA-E and for white matter lesions)
- Axial T2 Star/Gradient echo (GRE) (to assess ARIA-H, including superficial siderosis, and other hemorrhages
- Axial PD/T2: surrogate to FLAIR with better sensitivity in infratentorial regions
- Axial Diffusion-Weighted Imaging (for assessment of recent infarcts and white matter integrity examination). DTI may be performed at specific sites.
- Only in case of certain new findings on other sequence or at request of DMC: T1-weighted MRI with Gd-contrast.
- [redacted]

The duration of the MRIs will be approximately of a maximum of 52 minutes.

Centralized reading of the safety MRIs will be implemented through an Imaging vendor. The local site medical interpretation (by a radiologist or a neurologist or another qualified medical professional) will be used by the Investigator for immediate attention to clinically significant finding; however the assessment from the central reader will be captured in the database and used for reporting purposes. Therefore, MRIs are required to be scheduled at least 2 weeks before next drug administration/dispensing visit to verify safety findings before the injection (Cohort I) or the bottles are dispensed (Cohort II).

MRI scans will be archived as source documents at the Investigator's site. The de-identified MRI scans will be transferred by the site to the Imaging vendor (refer to the Imaging Manual provided by the Imaging vendor at study start).

Final interpretation, including assessment of ARIA (Sperling et al 2011) and white matter (Wahlund et al 2001) will be provided to the site by the Imaging vendor as source documents at the Investigator's site. Guidance to the Investigators in case of newly occurring findings is provided in Section 13.2.

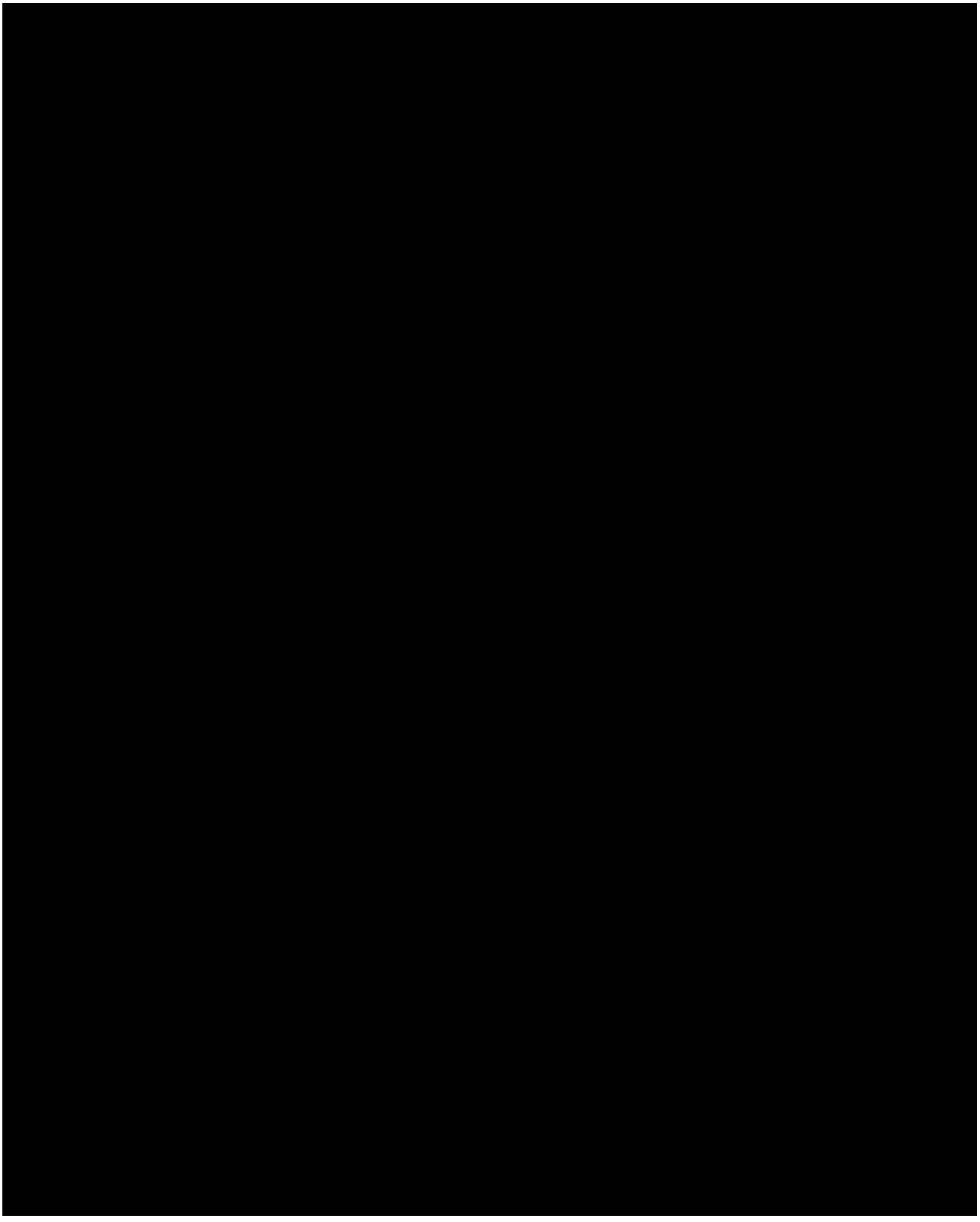
For participants who consent to the CSF sampling, the lumbar puncture will be done after the corresponding MRI scan. In case of MRI findings indicating inflammation, additional clinical investigations including physical and neurological examinations and laboratory evaluations will be performed (see Section 13.1).

In case of clinically suspected meningoencephalitis (e.g. drowsiness, fever, confusion, neurological signs, and convulsions), other autoimmune disease, or CNS inflammation, additional laboratory safety assessments, brain MRIs, and CSF analyses will be performed for safety reasons at any time during the study. In case a CSF sample is required for safety evaluation, the MRI scan will be performed before CSF sampling (see Section 13.1).

In case of new findings identified on MRI scans or if required by the DMC, gadolinium, a contrast agent, will be used at an unscheduled MRI T1 scan to investigate disruption of the blood-brain barrier as a sign of acute inflammation. In such case, gadolinium (e.g. Gadovist®-DPTA [0.1 mmol/kg]) will be injected as a slow bolus as per local product information. Creatinine clearance estimate will be checked by the Investigator before administration of gadolinium.

MRI findings will be reported additionally as AEs only if they induce clinical signs or symptoms that are considered clinically significant (i.e. asymptomatic ARIA that did not resolve at first follow-up scan and required missing of a scheduled injection), or require therapy (see Section 13.2)

Of note: Investigators may request an unscheduled MRI for safety purposes at any time during the study.



6.5.9 Appropriateness of safety measurements

Cohort I (CAD106 or placebo)

Brain MRIs will be conducted in all participants at Baseline and only participants without clinically significant findings may be enrolled. MRIs will be conducted at Screening, every 6 months for the first year (post-randomization) and then on a yearly basis. Overall, the frequency of MRIs is considered sufficient for CAD106, based on the absence of cases of meningoencephalitis, symptomatic ARIA findings or other immune reactions in previous studies. There will be no brain MRIs performed prior to the Month 6 MRI, based on the absence of clinically relevant findings at the Week 10 MRIs from previous trials and time required to develop an IgG antibody response. The brain MRI results at Month 6 will be reviewed prior to administration of the injection scheduled for Month 6. All brain MRIs will undergo central review and interpretation.

[redacted]

Laboratory assessments include monitoring of coagulation parameters to facilitate clinical decision making on potential use of anticoagulants and aid interpretation of any newly occurring cerebral micro- or macro-hemorrhages.

Other safety assessments are standard for clinical trials in populations of older individuals.

Cohort II (CNP520 or placebo)

Specific safety monitoring addresses the potential risks identified in the CNP520 repeat dose toxicity studies at high doses (CNS-related AEs observed in dogs and focal muscle atrophy in female rats) including monitoring of risks previously identified in BACE-1 and BACE-2 knock-out mice or reported for other BACE-1 inhibitors, such as potential for drug-induced vitiligo (hypopigmentation).

CNS-specific safety monitoring includes neurological examinations, safety brain MRIs, neuromuscular examination including muscle strength and cognitive function tests.

[redacted]

Given the imbalance of pruritus observed in a previous study, pruritus-specific questionnaires are planned to capture those AEs in a systematic way. Management of pruritus is described in Section 5.5.6.

Other safety assessments are standard for clinical trials in populations of older individuals.

To ensure participant safety and enhance reliability in determining the hepatotoxic or nephrotoxic potential of the investigational drug, a standardized process for identification, monitoring and evaluation of liver and renal events will be followed as described in Section 7.3 and Section 7.4.

6.6 Other assessments

6.6.1 Immune response (applicable to Cohort I only)

Detailed information on sample processing, labeling, and shipment in relation to immune response measurements will be provided in the Laboratory Manual supplied by the central laboratory prior to the start of the study.

The data will be provided in electronic form to the selected CRO. Since immune response data have the potential to unblind individual participants, the results from individual participants will only be communicated without participant identifications, with exceptions as listed under Section 5.4. Date and time of blood sample collection will be recorded on the requisition form provided by the central laboratory. If samples were not collected, the reason should be provided on the corresponding eCRF pages.

6.6.1.1 A-beta-specific antibody titers

Aβ-antibody response will be measured by determination of Aβ-specific IgG titers in serum using enzyme-linked immunosorbent assay (ELISA) methods.

Aβ-IgG titers will be determined in serum at scheduled visits from Screening up to End of Study. Aβ-IgG titers measurement will be performed prior to the investigational drug injection (samples taken pre-dose) at scheduled visits. In addition, if warranted to verify exposure for a CAD106-treated participant at any time (e.g. at unscheduled visits) or at a later time (after study completion and unmasking treatment allocation), follow-up samples may be taken and analyzed. In the later case, the results will not be captured in the clinical database, but will be described as a separate report as applicable.

[redacted]

6.6.1.3 A-beta - and Q-beta-specific T-cell lymphocyte response

T-cell studies are planned as a part of this study on a subset of at least 50 participants in Cohort I (CAD106 or placebo) at selected sites with personnel trained specifically on the collection process. In the Informed consent at these sites, volume of blood to be collected will be adapted correspondingly.

The objective is the characterization of Aβ- and Qβ-specific IFN-γ responses of T-cell lymphocytes following treatment with CAD106 using living peripheral blood mononuclear cells (PBMCs). The randomization ratio in the CAD106 cohort will be 5:3 (active vs. placebo). Hence, a total sample size of n = 50 will result in about 31 participants on CAD106. As of v05 of this protocol, no further samples are required.

Based on an event rate of 6% for meningoencephalitis as seen with AN-1792, (Orgogozo et al 2003), the probability of observing at least one case of Aβ-specific T-cell activation in 31 patients on active treatment, is 85.3%.

To evaluate T-cell response to the Aβ1-42 peptide, the Aβ1-6 peptide and the Qβ protein (positive control), specific Enzyme-Linked ImmunoSpot (ELISPOT) assays will be performed on PBMC samples at a central analytical laboratory specialized in such assays.

Peripheral blood sampling and PBMC isolation

Whole blood will be sampled at Baseline and Week 9 (two weeks after the 2nd injection) for peripheral blood mononuclear cell (PBMC) isolation. The samples will be kept at room temperature, protected from the light until shipment at ambient temperature using the specific shipment box and transporter on the day of collection. Each clinical center personnel will receive specific training on procedures for sampling and shipment of whole blood samples for PBMC isolation.

PBMC isolation will be performed at the selected laboratory according to specific instructions on blood sampling for PBMC isolation until shipment to the T-cell assay specialized laboratory.

In addition, in case of signs and symptoms of CNS inflammation or symptomatic ARIA-E, an unscheduled PBMC collection will be performed to test for T-cell activation in the identified participant as close to the event as possible and no later than 4 weeks after. This event-triggered additional sample for an individual participant who is experiencing the signs or symptom applies to any participant, i.e. will not be limited to the 50 participants included in the scheduled T-cell activation test.

6.6.3 Biomarkers

6.6.3.1 Imaging biomarkers

Radiologic evaluations of the brain will be performed using a standardized MRI protocol at screening and for safety and efficacy assessments. The data acquisition protocol includes pulse sequences for use in clinical safety evaluation. It also includes pulse sequences for secondary [redacted] analyses and for future use by members of the research community.

Specific details about the acquisition, processing, clinical interpretation, and quantitative analysis of all imaging exams will be included in the imaging charter. In addition, each modality will have a procedures manual that will be provided to the imaging centers with specific instructions for the acquisition of each imaging exam.

Cerebral amyloid burden and the effect of experimental treatment on cerebral amyloid will be assessed using an available amyloid PET tracer. ^{18}F-florbetapir is expected to be the primary PET ligand when available locally, unless its supply has potential logistical consequences (e.g., if production of ^{18}F-florbetapir impacts the scheduling of the PET scan, ^{18}F-flutemetamol or ^{18}F-florbetaben should be utilized instead, if locally permitted. In Germany, specifically, only ^{18}F-florbetaben is permitted as the amyloid PET tracer). For sites that cannot access any of the available amyloid PET ligands, amyloid levels in the CSF will be measured instead. See Section 6.6.3.2. [redacted]

Finally, tau PET will be performed to detect the effect of experimental treatment on neurofibrillary tangle burden, where locally permitted (i.e. not in Germany).

Volumetric MRI

The effect of CAD106 or CNP520 on brain volume (whole, regional and focal) will be assessed by means of T1 weighted, structural MRI scans performed as per schedule in Table 6-2, Table 6-3 and Table 6-4, if applicable. These scans will be part of the safety brain MRIs described in Section 6.5.6 above and performed on all participants. The change in volume of the hippocampus, lateral ventricles, and total brain will be measured specifically.

Procedural details will be provided to the participating imaging facilities in a separate document. Images will be analyzed centrally per the data analysis plan and archived.

Diffusion tensor and diffusion weighted Imaging

Diffusion weighted imaging will be acquired in all participants in order to be able to assist in assessment of recent infarcts. Diffusion weighted imaging will also be used to assess white matter integrity and in sites where it is technically feasible Diffusion Tensor imaging will also be added for this purpose. Further details will be given in the imaging acquisition manual.

[redacted]

PET scans

Amyloid and tau deposition and cerebral metabolism will be assessed using a PET/CT scanner meeting requirements specified in the PET Imaging manual. Amyloid, PET and tau PET scanning procedural details will be provided to the participating PET imaging facilities in a separate document. The same scanner should be used for each participant for all PET evaluations throughout the study. Images will be analyzed centrally per the data analysis plan and archived. If PET images are acquired during screening, and there is a risk that the image to be acquired at year 2 may not allow for longitudinal analysis (e.g. change on scanner), the year 2 scan should be skipped to protect participant from unnecessary radiation exposure.

All tracers used for the PET scans are radiolabeled with ^{18}F, and will be delivered to the participant as an intravenous bolus injection at the PET site. The site will communicate the height and weight of the participant. The approximate target activity is specified below for each type of scan.

The approximate scanning time, during which the participant will be lying on his or her back, will be 10 to 30 minutes depending on the PET tracer. Participants will be supervised during each PET-scan. CT scans may be used to correct the PET images for radiation attenuation and scatter. After the PET-scan has been completed, participants will be allowed to leave the PET center if there are no prohibitive findings or events, as assessed by a physician.

Since PET scan data have the potential to un-blind individual participants, the results will be imported into a restricted database with controlled access and managed as described in Section 5.4. The PET scan images, including the baseline scan, are also not intended to be shown to participants while the study is ongoing.

Amyloid PET

Amyloid PET will be performed in all participants at Screening and Month 24 (unless site cannot access an amyloid PET tracer). Another assessment at Month 60 will only be performed in participants who consent to the additional biomarker assessment.

Locally permitted PET tracer utilized (e.g. ^{18}F-florbetapir, ^{18}F-flutemetamol or ^{18}F-florbetaben), date, time, batch, volume, and radiation dose of the injection for each scan (according to the Imaging manual) and any AEs occurring at the PET center will be recorded on the eCRF.

Cerebral-to-reference region standard uptake value ratios (SUVRs) will be calculated using pre-defined and automatically generated cerebral and reference regions-of-interest.

If amyloid PET tracer is not available locally, refer to Section 6.6.3.2.

Tau PET

Tau PET, where available, is voluntary and requires a specific consent. Tau PET will be performed to detect the effect of experimental treatment on neurofibrillary tangle burden. The same locally permitted radiotracer (^{18}F-flortaupicir (AV-1451), MK-6240 or PI-2620) will be used for all scans of a given participant. Corresponding documentation will be submitted, if required (i.e. not in Germany).

At the subset of sites that can access the selected tau PET tracer and have the required imaging capability, participants who consent to an additional PET scans will have tau PET scans performed at Screening, Month 24, and Month 60. In locations where compliance with total radiation exposure limits could be of concern, or in case of consent to a single additional voluntary PET scan, tau PET scans is to be prioritized [redacted].

Date, time, batch, volume, and radiation dose of the injection for each scan (according to the Imaging Manual) and any AEs occurring at the PET center will be recorded on the eCRF.

SUVR measurements will be calculated in pre-defined cerebral and reference regions, which will be predefined based on their ability to detect and track AD-related tangle burden in independent observational data sets. [redacted]

[redacted]

Data will be analyzed to determine the change in regional glucose metabolism, relative to the selected reference region, as noted above.

6.6.3.2 Fluid biomarkers

For countries that cannot access any of the available amyloid PET tracers, CSF measurement of Aβ / tau levels at screening is mandatory, however, the results are not required to be verified for eligibility. Additionally, if the PET images acquired at year 2 may not allow for longitudinal analysis of the required quality, the scan should be skipped to protect participant from unnecessary radiation exposure, and consent to CSF collection be strongly encouraged.

At the remaining visits for the above, and at all visits in other participants, CSF and blood samples will be collected from consenting participants to assess AD-related fluid biomarkers as part of secondary [redacted] objectives.

Timing of sampling of CSF and blood for AD biomarkers is listed in Table 6-2, Table 6-3 and Table 6-4, if applicable.

On dosing days, blood and CSF samples will be collected prior to study drug administration unless otherwise specified. For additional information on sample processing and labeling, refer to the Laboratory Manual supplied by the central laboratory prior to the start of the study.

[redacted]

detection and/or tracking of AD; to improve the understanding of the biology of AD; for [redacted]; to help in the discovery of new treatments; to provide a resource for genome wide association, sequencing, epigenetic, and gene expression studies; and/or to support research studies unrelated to Alzheimer's disease).

Participants will be asked to provide specific consent for such extended usage and option to share their samples with the scientific community under management from an independent committee. A specific process for sharing samples with other academic laboratories will be described in a separate charter.

Samples will be sent to central repositories, including the Novartis Clinical Repository (NCR) and the National Cell Repository for Alzheimer Disease (NCRAD), for extraction of genetic material, storage, and eventual distribution.

Since biomarker data have the potential to unblind individual participants, the results will be imported into a restricted database with controlled access and managed as described in Section 5.4.

Participation in CSF collection for analysis of AD-related biomarkers is encouraged, but not mandatory and will require a specific consent. However, if amyloid PET is not assessed, CSF collection is mandatory at Screening.

For each participant, best efforts should be exerted to perform subsequent LP's at the same time of day as the baseline LP (in case it was not performed in the morning, then perform follow-up LPs at the same time of the day).

Within the biomarker assessments, several target engagement and disease-related fluid biomarkers, including $A\beta_{1-40}$, $A\beta_{1-42}$, total-tau and phospho-tau_{181} and light chain neurofilaments (NFL) in CSF will be assessed.

[redacted]

For Cohort I samples, the interaction with CAD106-induced Aβ-specific antibodies will be accounted for in the assay method and concentration calculation.

Blood-based biomarkers

Blood samples will be collected to explore blood biomarkers including gene expression associated with the treatment response to CAD106 and CNP520, respectively, and the pathophysiology of AD and/or associated diseases. Serum and plasma samples will be collected at time points of the safety labs blood draws. Samples will be prepared and shipped according to procedures described in the Central Laboratory Manual.

Within the biomarker assessments, several target engagement and disease-related fluid biomarkers, including $A\beta_{1-40}$ in plasma and NFL in plasma/serum will be assessed [redacted] for Cohort II.

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) that occurs in a participant **after they have provided written informed consent** for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Similarly any untoward medical occurrence associated with genetic disclosure in this study will be captured as an AE.

All SAEs and AEs should be collected from the time of signature of Informed consent #1. Table 7-1 provides the guidelines for reporting of AEs and SAEs in the study.

Table 7-1 SAE and AE capture and documentation

Participant status	AE reporting	SAE reporting
ICF#1 Part 1B signed but not randomized to treatment	Only events deemed related to genetic disclosure (until final visit of genetic disclosure follow up)	Only SAEs deemed related to genetic disclosure (until final visit of genetic disclosure follow up)
ICF#2 signed but not randomized to treatment	All events	All SAEs deemed related to genetic disclosure (until final visit of genetic disclosure follow up) SAEs not deemed related to genetic disclosure: Only captured from signing of consent to 30 days after date of Screening Failure
Randomized to treatment	All events	All SAEs Cohort I: until 1 year after last study visit; SAEs after 30 days after last study visit recorded only in safety database Cohort II: until 30 days after last study visit

The occurrence of AEs should be sought by non-directive questioning of the participants at each visit during the study. Adverse events also may be detected when they are volunteered by the participants during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least 1 of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require medical intervention

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are considered to be non-typical in participants with underlying disease. Investigators have the responsibility for managing the safety of individual participants and identifying AEs. Alert ranges for labs and other test abnormalities are included in Section 13.2.

Refer to Section 7.7 for additional guidance on adverse events that may be related to genetic disclosure and Section 6.5.8.2 for additional guidance on pruritus.

Adverse events should be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

The following severity grades will be used:

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

All AEs should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)
- study investigational treatment permanently discontinued due to this AE
- concomitant medication given
- non-drug therapy given
- participant is hospitalized/participant's hospitalization is prolonged

The AE outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown) should be recorded.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the participant's informed consent and should be discussed with the participants during the study as needed.

The Investigator should also instruct each participant to report any new AE (beyond the protocol observation period) that the participants, or the participant's personal physician, believe might reasonably be related to the investigational treatment. This information should be recorded in the Investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to the local Novartis safety desk.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any AE (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - is medically significant, i.e. defined as an event that jeopardizes the participant or may require medical or surgical intervention, including Appendix 1.3: Clinically notable SAEs that require discontinuation of treatment .

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or, development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a SAE.

7.2.2 SAE reporting

To ensure participant safety, every SAE, regardless of causality to study drug treatment or genetic disclosure, occurring after the participant has provided informed consent (Refer to Table 7-1) and for 30 days after the last study visit (EoS or PPW) must be reported to Novartis safety within 24 hours of learning its occurrence Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Any SAEs experienced after the 30 day period after the last study visit (EoS or PPW) for Cohort II or last telephone call from the one year Extended safety monitoring for Cohort I should also be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported SAE should be reported separately as a new event.

Cohort I (CAD106) only:

Extended safety monitoring for 1 year is required for Cohort I due the potential persistence of antibody titers. Any SAEs occurring during the 1 year extended monitoring (and after 30 day window after the last study visit), the SAE will only be captured in the safety database and not in the clinical database/eCRFs.

At the study completion or upon early termination, all Cohort I participants will be followed for an extended safety monitoring over 1 year. The extended SAE collection after study completion / premature patient withdrawal will be handled by the investigator through telephone calls to the participant, study partner and/or general practitioner, every 3 months. These telephone calls and the participant current condition and recent history since last telephone call will be documented in the participant's charts. The correspondence between the investigator and the medical team involved in assessing the participant's safety (e.g. radiologist, GP) will be archived as source documents. Visits to the site may be organized by the investigator as required to monitor the participant's safety according to his/her usual clinical practice.

During the extended SAE collection, the participant is no longer bound to the criteria defined in this clinical study protocol. In particular, no limitations in concomitant medications or other therapies will be required any longer.

At the end of the extended SAE collection period (see Section 3.1.2.4), the investigator will be contacted by Novartis to confirm the outcome of any unresolved SAEs and the latest available participant health status. The SAEs reported during the 1-year extended safety monitoring will only be collected in the Novartis safety database. The information of SAEs reported in this period will be summarized in an addendum to the Clinical Study Report and reported to all Health Authorities where required.

In case participants from Cohort I get re-randomized to Cohort II (see section 5.5.9) the safety monitoring will be captured within the study visits and do not require separate phone calls.

Any SAEs experienced after this one year period should only be reported to Novartis if the investigator suspects a causal relationship to the investigational treatment drug.

SAE collection

Information about all SAEs (either initial or follow up information) is collected and recorded in English on the electronic Serious Adverse Event Report (eSAE) Form within the Oracle Clinical/Remote Data Capture (OC/RDC) system (wherever available and/or feasible) or on the paper SAE Report Form that should be used as back-up, especially in case where there is no feasibility of the use of eSAE Form.The Investigator must assess the relationship of each SAE to study treatment (CAD106 or CNP520).

SAEs (initial and follow-up) that are recorded electronically in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Chief Medical Office and Patient Safety (CMO&PS) immediately after investigator signature or 24 hours after entry, whichever occurs first.

Follow- up information is submitted as instructed in the investigator file. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the participant continued or withdrew from study participation.

If the SAE is not previously documented in the IB and is thought to be related to the investigational treatment a Pharmacovigilance Department associate may urgently require further information from the Investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events will be followed.

The following two categories of abnormalities will be considered AEs during the course of the study and reported as such:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter(s)
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver eCRF pages

Please refer to Table 13-7 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 13-7 of Appendix 1.5 will be followed up by the in Investigator or designated personnel at the trial site as summarized below. Detailed information is outlined in Table 13-8

For the liver laboratory triggers, liver function tests (LFTs) will be repeated within the next week to confirm elevation.

These repeat LFTs will be performed using the central laboratory, if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the participant. Repeat laboratory tests will then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver eCRF pages.

If the elevation is confirmed, close observation of the participants will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the participants if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, and hepatologist consultation, based on Investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate eCRF pages, including the liver event overview eCRF pages.

7.4 Renal safety monitoring

To ensure participant safety and enhance reliability in determining the nephrotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of renal events will be followed.

The following two categories of renal abnormalities will be considered and reported as AEs during the course of the study:

1. Serum event:
    - Confirmed (after ≥ 24 h) increase in serum creatinine of ≥ 25% compared to Baseline during normal hydration status
2. Urine event
    - New onset (≥ 1+) proteinuria, hematuria or glycosuria; or
    - Doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

Please refer to Table 13-9 for complete definitions of renal laboratory triggers and renal events. Every renal laboratory trigger or renal event should be followed up by the Investigator or designated personnel at the trial site as summarized in Table 13-9 .

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE, and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-2 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

Participants eligible for this study will be 60 to 75 years of age, and women of childbearing potential are excluded from the study. Fertility in this age range is therefore not within the scope of this study.

7.7 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The scale must be administered on site, at each visit, including unscheduled visits.

A validated shorter electronic version called eC-SSRS will be used to capture self-reported C-SSRS data by the participant via a web-based system. The eC-SSRS is a participant self-reported outcome assessment (PRO) that uses a detailed branched logic algorithm evaluating each participant's suicidality ideation and behavior in a consistent manner. At the conclusion of each assessment, the Investigator will receive a detailed eC-SSRS Findings Report via e-mail or fax. The investigator will review the report before the participant is discharged and leaves the site. If the system assesses the participant as having positive suicidal signs, the Investigator will be immediately notified by either fax, email and/or via telephone.

If, at any time, the score is "yes" on item 4 or item 5 of the Suicidal Ideation Section of the eC-SSRS (and if at Screening, the ideation occurred in the past 6-months) or "yes" on any item of the Suicidal Behavior Section, the participants must be referred to a psychiatrist for further assessment and/or treatment, if the investigator is not a certified psychiatrist. The decision on whether the investigational treatment should be discontinued is to be taken by the Investigator in consultation with the psychiatrist to whom the participant is referred.

Based on investigator judgement of the participant ability to complete the eC-SSRS on his own, e.g. in case of progression to dementia, the supplemental C-SSRS data eCRF page may completed instead with input from the study partner.

In addition, all life-threatening events should be reported as SAEs. For example, if a participant answers "yes" to one of the questions in the Suicidal Behavior Section, an SAE must be reported.

All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the Suicidal Behavior Section) should be reported as AEs and assigned the appropriate severity grade.

All SAEs relating to suicidal behavior should be reviewed by the DMC.

7.10 Meningoencephalitis monitoring

To ensure participant safety and enhance reliability in determining the meningoencephalitis potential of an investigational drug, a process for identification, monitoring and evaluation of meningoencephalitis, or other severe immune reaction events will be followed.

Cases of meningoencephalitis will be considered and reported as clinically notable SAEs during the course of the study

Please refer to Section 13.1 for recommended test for suspected cases of meningoencephalitis and reporting procedures.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol and eCRFs with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant's records, review I/E criteria, the ICFs signature and date, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that investigational treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized CRO. Additionally, a central analytics organization may analyze data, identify risks and trends for site operational parameters, and provide reports to Novartis and the selected CRO to assist with trial monitoring.

The Investigator must maintain source documents for each participants in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on the eCRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. The Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion and exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the EDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigational site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomic Therapeutic Chemical (ATC) classification system. Concomitant procedures, non-drug therapies and AEs will be coded using the MedDRA terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis. ECG readings will be processed centrally and the results will be sent electronically to Novartis.

MRI images will be read centrally for safety evaluation and volumetric measures of brain regions. The results will be sent electronically to Novartis. The PET imaging data from amyloid [redacted] will be analyzed centrally. The results will be sent electronically to Novartis.

All clinical scales administered by the clinician or self-reported by the participant or the informant will be collected on an eSource (Virgil® tablet) provided by the Cognition vendor who will also manage the database. The database will be sent electronically to Novartis with the exception of the audio recordings.

Diary data will be entered by the participant into an electronic diary hosted on a web platform or via an IRT system. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis.

Photographs will be sent by the site to the central dermatology imaging vendor if there are treatment emergent skin AEs. Only reports (not photographs) from the central dermatologic imaging vendor will be sent electronically to Novartis.

Randomization codes and data about all investigational drug(s) administered or dispensed to the participants and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be reported. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

[redacted]

8.4 Data Monitoring Committee

The independent DMC will review the unblinded efficacy, safety, and tolerability data from all participants on an ongoing basis. Regular meetings will be scheduled on an approximately bi-annual basis starting when safety data from first participant first post-treatment visit is available, and additional *ad hoc* meetings or off-line consultation may be scheduled if needed.

The DMC will be expected to provide recommendations to enhance safety monitoring, suspend treatment and/or stop the trial or a specific Cohort in case of (1) unexpected safety issues, (2) futility, or (3) outstanding efficacy. If the DMC recommends the suspension of treatment for the current CNP520 dose of 50 mg daily in Cohort II, the sponsor may then activate the DRM, in consultation with the DMC.

The DMC may also assess any potential relationship (i.e. temporal) between the antibody titers of CAD106 or [redacted] data for CNP520 with the occurrence of a particular AE of interest at the participant level, or identify signs or signals of safety concerns across the study.

The DMC will also receive all SAEs, specific reports (including CDR, RBANS, MMSE and NPI-Q, centralized safety MRI scans), T-cell activation results (including event-triggered unscheduled time-point) and any other reports as agreed in the DMC charter, regardless of their relationship to study medication. The DMC may then access the treatment codes as provided in the DMC closed reports for each participant, as required to assess the relationship to study medication and asses criteria for suspension according to the current DMC Charter, applicable until treatment termination.

The DMC will be provided with individual participant's data (unblinded), as well as summaries and graphs as appropriate. The tables, listings and graphs will be prepared by independent statisticians and statistical programmers who are not otherwise involved in the planning and conduct of the trial. Content and format of the tables, listings, and graphs will be agreed with the DMC.

The DMC will be composed of recognized academic experts and will be assisted by an independent statistician and programmer.

8.5 Progression Adjudication Committee

A process for the adjudication of MCI/dementia diagnoses will be implemented with an external Progression Adjudication Committee (PAC) managed by the Cognition vendor. Details of the diagnostic criteria are described in Section 6.4.1 and a description of the PAC members, role, and function will be described in a specific charter applicable until treatment termination.

The communication steps between the site and the PAC as well as key coordinating roles from the Sponsor and the Cognition vendor will also be detailed.

The PAC will be provided with the available participant data to assess for possible progression and potential confounding factors.

Adjudication data will be collected and maintained by the Cognition vendor, and transferred to Novartis at pre-defined frequency.

8.6 Disclosure Monitoring Advisory Group (DMAG)

The DMAG is responsible for assisting the DMC in an advisory capacity, monitoring the safety of the participants in relation to the genetic disclosure. The responsibilities of the DMAG, as also outlined in the DMAG Guidelines, are:

- Reviewing the outputs (e.g. table/figure/listing of the data from the relevant scales, adverse events (AE) and serious adverse events (SAE) reports (those deemed related to genetic disclosure)) and making recommendations regarding changes or adjustments (including limiting the disclosure follow-up to 2-7 days in non-HMs)
- Providing summary reports to the DMC prior to each data review meeting summarizing any findings related to the safety monitoring of genetic disclosure.

The DMAG will be composed of recognized academic experts, as described in the DMAG Guidelines.

9 Data analysis

The final analysis for each respective cohort will occur once the targeted number of events for the cohort has been reached and all participants have completed their month 60 assessment. The final analysis of the cohort which completes earlier will be performed first and independently from the final analysis of the other cohort. Specific analyses which involve data from both cohorts together will be performed when both cohorts are completed. The details of the final statistical analyses are described in the Statistical Analysis Plan (SAP).In general, data will be reported by treatment arm. Summaries including only baseline data, may also present a total group (all participants). In case of DRM in Cohort II, summaries may also include the sub-group of participants randomized to the active treatment arm after the DRM, i.e. those who started on the LDR. Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables for each cohort. The number and percentage of participants in each category will be presented for categorical variables for each cohort.

In Cohort II, the primary treatment arms for efficacy analysis will include the following participants based upon whether or not the DRM has been implemented.

- In the case that the DRM does not occur, the 2 treatment arms would remain the same as planned originally. The primary treatment arms are CNP520 50 mg once daily or matching placebo in a respective ratio of 3:2. The primary treatment arms include participants who received either CNP520 50 mg once daily or matching placebo. In this case, the primary active arm is Arm #3, i.e. the CNP 50 mg once daily active arm.
- In case the DRM is implemented, the same randomization ratio is maintained, 3:2 active versus placebo. The primary active arm (Arm #3) consists of the following participants:
  - Those who received CNP520 50 mg once daily dose followed by CNP520 LDR (those who were originally randomized to 50 mg once daily, and subsequently switch to the lower dose regimen),
  - Those who received CNP520 LDR dose only (those who were randomized to active treatment arm after the DRM).
- The primary placebo arm (Arm #4) consists of all the participants who have been randomized to Arm #4 and received placebo regardless of DRM.

9.1 Analysis sets

The Randomized analysis set (RAS) will consist of all participants who received a randomization number, regardless of receiving study medication.

The Safety analysis set (SAF) will consist of all participants who have started study medication and have had at least one safety assessment after first dose administration.

The Full analysis set (FAS) will consist of all randomized participants who started study medication.

In general and if not otherwise specified, efficacy analyses will be conducted on data from participants in the FAS, safety analyses will be conducted on data from participants in the SAF.

Cohort I Only

The modified FAS (MFAS) will be defined as the subset of the FAS which excludes the serological non-responders (NR) to CAD106.

The classification of participants into Serological Responders (SR) and serological NR to CAD106 will be based on the individual CAD106-induced Aβ-specific IgG titer values in serum. The classification rules have been developed on available data from previous Phase II studies.

Participants of the CAD106 cohort will be classified in the following categories: Placebo, NR, SR. SR will be defined in the following way based on titer assessments up to and including Week 26 of the Treatment Epoch:

Participants whose Aβ-specific IgG titer in serum is both greater than 16 units after 2nd and before 3rd injection and greater than 3 times the LLOQ (LLOQ=8.93 units as determined in the phase II program, 3*LLOQ=26.8 units) after the 3rd injection.

NR will be participants that do not meet the SR definition.

9.2 Participant demographics and other baseline characteristics

Demographic variables and other Baseline characteristics will be summarized for each treatment arm and all participants (total).

In addition, all relevant medical history will be summarized following the same strategy.

9.3 Treatments

For Cohort I (CAD106 or placebo), a data listing and a summary of the administered investigational drug injections will be provided. In addition, serological responder rates and summary parameters for serum Aβ-specific IgG titers will be tabulated.

For Cohort II, data for investigational drug administration will be summarized and listed. In case of DRM, summaries will also include the sub-group of participants randomized to the active treatment arm after the DRM, i.e. those who started on the LDR.

The number and percentage of participants receiving concomitant medications and significant non-drug therapy will be summarized by preferred term (coded by WHO Anatomic Therapeutic Chemical classification [ATC]) and by treatment arm, and be listed.

9.4 Analysis of the primary variable(s)

For each investigational drug, the primary analysis will contrast each primary active treatment arm vs. matching Placebo based on the FAS.

There are two primary endpoint variables: TTE, with event defined as diagnosis of MCI or dementia due to AD, and the APCC test score. Both endpoints are considered to be clinically relevant. Success of the trial will be determined independently for each investigational drug by a positive result **in at least one** primary endpoint. In addition, each cohort will undergo an Interim Analysis based on data from the two primary endpoints. To control the overall family-wise type I error rate within cohorts for testing two endpoints at two points in time, an appropriate multiplicity adjustment will be applied to the analyses of the primary efficacy

variables. The strategy to adjust the overall family-wise type 1 error (α = 5%) is described in Section 9.7.

9.4.1 Variable(s)

Two primary variables will be used:

- TTE, defined as the time from randomization to the first event that is the first confirmed diagnosis of MCI or dementia due to AD. The criteria for diagnosis and confirmation are specified in Section 6.4.1. The date of the initial investigator diagnosis will be used to establish the date of the event (not the date of the confirmation). In case no confirmed event has been observed for an individual, the observation will be censored, and the censoring date will be defined as the last date when the diagnostic classification has been assessed. Time to censoring date will also be calculated from the date of randomization.
- APCC test score change from baseline to Month 60.

The APCC test score is defined as a weighted sum of the following test items:

- Raven's Progressive Matrices – subset
- MMSE:
  - Orientation to Time
  - Orientation to Place
- RBANS:
  - List Recall
  - Story Recall
  - Coding
  - Line Orientation

The range of the APCC test score is from 0 to 100 where higher scores correspond to better cognitive performance. The APCC will be derived based on the test items using the formula: APCC test score = 1.360*RBANS List Recall + 1.100* RBANS Story Recall +1.390* Raven's Progressive Matrices (subset) + 0.321*RBANS Coding + 0.510*RBANS Line Orientation + 2.140*MMSE Orientation to Place + 2.240*MMSE Orientation to Time.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary analyses will consist of testing hypotheses related to the 2 active investigational drugs. The primary analyses will compare primary active vs. matching placebo in both cohorts separately, i.e. the primary analysis will consist of testing hypotheses related to the 2 investigational drugs. As the design includes separate placebo arms in each of the 2 cohorts, these are considered as independent comparisons similar to the testing in 2 independent trials. As a consequence, an adjustment of the type one error rate to account for the multiple testing in the two cohorts is not needed. For Cohort II, the same primary objective and hypotheses will be applied to the primary active arms.

For each of the two investigational drugs, the following two null hypotheses will be tested corresponding to the two primary endpoints:

- H_{01}: The primary active treatment arm does not differ from matching placebo with regard to the distribution of time to first diagnosis of MCI or dementia due to AD;
- H_{02}: The primary active treatment arm does not differ from matching placebo in the mean change from Baseline to Month 60 in the APCC test score;

The corresponding alternative hypotheses are:

- H_{11}: The primary active treatment arm differs from matching placebo with regard to the distribution of time to first diagnosis of MCI or dementia due to AD.
- H_{12}: The primary active treatment arm differs from matching placebo in the mean change from Baseline to Month 60 in the APCC test score.

The type one error rate is $\alpha = 5\%$, an appropriate multiplicity adjustment will be applied to the analyses of the primary efficacy variables within cohorts (Section 9.7).

The final primary analysis of the TTE endpoint will be performed only once the target number of events has been reached in the respective cohort and after all participants in the cohort have reached 60 months of follow-up (whichever occurs later) unless they discontinued prematurely. Any data collected after the cut-off date will not be used for the primary analysis of TTE. That means specifically that only confirmed events collected up to the data cut-off date will be counted. Confirmation information collected after the cut-off date confirming an earlier (meaning before the cut-off date) diagnosis of MCI or dementia due to AD will not be taken into consideration. As a consequence, the observation will be censored, and the non-confirmed diagnosis will not be counted as an event.

The time required to observe the target number of events is estimated to be close to the 60-month duration required for the APCC test score primary outcome. In case the target number of events needed for the final TTE analysis has not been reached when the last participant completes the 60 months follow-up, a decision will be made whether the follow-up time will be prolonged or whether the final analysis will be carried out earlier. The final primary analysis of the APCC score will be performed after all participants reached 60 months of follow-up, but all available data will be included in the final analysis.

The primary analysis of the TTE endpoint will be based on a Cox proportional hazards (PH) model including treatment group (primary active treatment arm or matching placebo) as a factor and adjusted for important baseline covariates.

Terms will be included for the following effects:

- treatment group
- baseline value of the APCC test score
- age group at baseline
- region
- baseline amyloid load.

The primary analysis of the APCC score will be performed using a longitudinal model for the change from baseline: the mixed repeated measure model (MMRM).

An unstructured covariance matrix will be assumed, and the model will include the following fixed effects:

- treatment group
- time as the discrete variable scheduled (mapped) visit
- baseline value of the APCC test score
- age group at baseline
- region
- baseline amyloid load,

and the following interaction terms:

- treatment group × visit
- baseline APCC test score × visit
- baseline amyloid load × visit.

The adjusted least square means (LSM)s of change scores for each treatment group, the difference between the LSMs (active vs. placebo), the 95% confidence intervals and the unadjusted 2-sided p-values, comparing the active and placebo LSMs, will be calculated from the MMRM analysis and presented for each visit.

9.4.3 Handling of missing values/censoring/discontinuations

Primary endpoint time-to-diagnosis of MCI or dementia due to AD

In general, an observation will be censored if no event has been observed at the TTE analysis cut-off date. The censoring date will be defined as the last date where the TTE endpoint has been assessed.

The censoring date for each participant that did not have an event (i.e., a confirmed diagnosis) is defined as follows:

1. For participants ongoing in the study without a confirmed diagnosis at the time of the cut-off: the last day of a diagnosis assessment (the previous visit where a diagnosis assessment occurred prior to the cut-off date).
2. For participants who permanently discontinued from the study prior to the cut-off: The last day of a diagnosis assessment prior to study discontinuation.

The primary analysis method (Cox proportional hazards model) for the TTE endpoint is valid and consistent under a censored at random assumption, i.e. the probability of censoring is independent from the event (MCI or dementia due to AD).

Sensitivity Analyses

The robustness of the primary analysis results for the TTE endpoint will be further explored through sensitivity analyses using tipping point and controlled imputation approaches and under a plausible censoring not at random (CNAR) process. Scenarios for which these analyses will be conducted include:

1. Data collected off-drug, i.e. beyond 12 weeks after permanent discontinuation of study drug;
2. Missing data from participants who prematurely discontinued the treatment epoch due to an AE, death, or unsatisfactory therapeutic effect (UTE).

Explicit details will be further described in the SAP.

The Cox PH model will be repeated including the time × treatment interaction which serves also to investigate the assumption of proportional hazards. These explorations will be complemented by graphical methods based on Kaplan-Meier plots and plots of the log-log survivor functions.

In conjunction with the primary analysis Cox PH addition, a stratified log-rank test stratified for a selection of most critical baseline covariates may be performed in case there are no empty or sparse cells. Stratification factors are selected from the following list:

- baseline value of the APCC test score (dichotomized)
- age group at baseline
- region
- baseline amyloid load (dichotomized)

An analysis corresponding to the primary analysis method will be conducted, but using the Investigator's diagnosis to identify events based on two consecutive diagnoses by the investigator.

Primary endpoint APCC

This section includes discussion on the methodology for handling composite APCC scores that are either incalculable due to inadequate availability of the underlying components, or are completely missing for a participant at a particular visit.

The methodology for handling missing individual item components that contribute to the composite APCC score for a participant at each visit will be described in full detail in the SAP.

The primary analysis method (MMRM) for APCC test score is valid and consistent under a MAR assumption, i.e. given the observed data (responses and covariates) the probability of drop-out does not depend on the unobserved responses.

For the following scenarios it is plausible not to regard the corresponding missing data as MAR:

- Missing data after conversion to MCI or dementia due to AD,
- Data collected off-drug, i.e., beyond 12 weeks after permanent discontinuation of study drug,
- Missing data due to an AE, death, or UTE.

To address missing data which may be not MAR, the following sensitivity analyses will be applied:

- Tipping point analysis where a penalty to imputed MAR scores will be applied from the point onwards when the missing data fit any of the above mentioned reasons.;
- Controlled imputation approach: within each treatment arm, the imputation model is built based on data from participants in the same arm who also had a similar disease progression but who remained in the study ('retrieved data'). Such an analysis would only be possible if sufficient retrieved data are available to build an imputation model.

The robustness of the primary analysis results for the APCC endpoint will be further explored through a sensitivity analysis under a plausible missing not at random (MNAR) process.

For this sensitivity analysis, missing values in the active arm will be imputed using a so-called 'copy reference' imputation approach assuming that participants discontinuing due to AE, death (D), or unsatisfactory therapeutic effect (UTE) behave like participants from the placebo arm after study discontinuation.

Missing data for other reasons and for all placebo arm participants will be imputed under a MAR assumption, that is missing data are imputed based on the treatment-specific information for the repeated measurements and covariates.

For each imputed and thus completed data set, the primary analysis model is then fitted as specified in Section 9.4.2. The resulting sets of parameter estimates and associated covariance matrices are then combined to derive overall estimates, confidence intervals that adequately reflect missing data uncertainty, as well as associated p-values using Rubin's rules (Little and Rubin 2002).

9.4.4 Supportive analyses

Analyses on the MFAS for Cohort I (CAD106)

For Cohort I (CAD106 or placebo), the primary analysis will be repeated based on the MFAS, i.e. the FAS excluding serological non-responders as primary supportive analyses to strengthen the interpretation of the primary analysis.

This is based on the assumption that the response to treatment will be driven by the serological response to CAD106. Hence, the primary supportive between-group comparisons of the primary endpoint will be performed between SRs and placebo for benefit assessment. Although there is no rationale that potential serological non-responders may have a different natural course regards the primary endpoints as compared to potential SRs, these analyses will also take into account that participants in the control group would potentially have not shown serological response if they had been on active treatment. This approach will follow the method presented by Koepsell et al (2007) and is based on the assumption that the treatment effect is estimated most appropriately by comparing the participants who did respond to active immunization with the participants in the placebo arm who would have responded to active immunization. Although, these participants cannot be determined, based on some assumptions, the mean effect of the potential SRs in the placebo arm can be estimated from the available data.

Comparison versus pooled placebo

Comparisons of the active investigational drugs versus the pooled placebo group, i.e. pooling the placebo arms from both cohorts, will be performed as an additional primary supportive analysis for both investigational drugs once both cohorts are completed (i.e., study has completed). For both investigational drugs, the primary analysis will be repeated, but using the pooled placebo arm as control group instead of matching placebo.

The difference in mode of administration, quarterly injections vs. one daily oral capsule, is not expected to have an impact on the primary endpoint and is thus not assessed as a major issue for the primary analysis based on pooled placebo. Nevertheless, possible cohort effects will be investigated, specifically due to the time lag for start and finish of the two cohorts or due to the pause in Cohort I allocation for the CNS activity futility IA. The two placebo groups will be evaluated to determine whether there is a significant imbalance with regards to any relevant characteristic.

Censoring data after discontinuation of study drug

Comparisons of the active investigational drugs versus the matching placebo group will be performed for both investigational drugs on the FAS, taking into account whether a participant had continued, interrupted or permanently discontinued study-drug during the study. The same statistical methods as for the primary analysis will be implemented, i.e. with regard to the analysis model and the MAR assumption for missing data. For the Cohort I (CAD106), data collected later than 6 months after discontinuation from study drug will not be included in the supportive analysis. For Cohort II (CNP520), data collected later than 3 months after discontinuation of study drug will not be included.

Similar analyses will also be specified for insufficient exposure (i.e. for participants who did not take treatment for cumulative missed doses of more than 26 weeks (Cohort II) or >2 injections (Cohort I) during the course of the study.

Other analyses of the time-to-event endpoint

A non-stratified log-rank test will be conducted to compare estimates of the hazard functions of the treatment groups at each observed event time.

A model including the additional treatment group × baseline amyloid load interaction will also be implemented as an important primary supportive analysis.

Other analyses of the endpoint APCC

The primary analysis of the APCC test score will be supported by the following important primary supportive analysis: An MMRM is based on the same assumptions as the primary analysis model and including the same factors, but also the additional interaction terms

treatment group × baseline amyloid load

treatment group × baseline amyloid load × visit.

An MMRM adjusted for a broader range of possible confounding factors such as site, gender, years of education, and hippocampal volume will also be implemented. Another MMRM based approach will investigate the average contrast over years 5 to 8.

In addition, the primary analysis will be supported by an MMRM similar to the primary model, but introducing time as a continuous factor. The interpretation of results from the primary analysis will also be supported by the investigation of change in treatment effects over distinct time periods.

Potential drug-drug-interaction (DDI)

Potential PD-mediated DDIs with frequent concomitant medications may include the use of cholinesterase inhibitors and/or another prescription AD treatment (e.g. memantine) in terms of transient interaction with cognitive readouts.

Treatment interaction with CAD106 and CNP520 will be assessed as follows:

- The primary efficacy analysis will be based on an intention-to-treat principle and will neither exclude participants who started ChEIs and/or another prescription AD treatment (e.g. memantine) during the study, nor exclude time points from the analysis after start of ChEIs and/or another prescription AD treatment (e.g. memantine).
- Sensitivity analysis will be carried out to investigate the role of concomitant cholinesterase therapy and/or another prescription AD treatment (e.g. memantine) on the efficacy of CAD106 and CNP520, such as exclusion of time points from the analysis after initiation of ChEI therapy and/or another prescription AD treatment (e.g. memantine), or using this information as a stratification factor or as a time-varying covariate in statistical models.

Sub-group analysis

In case of DRM, analyses similar to the primary analyses will be performed on the subset of the FAS defined as participants who have been randomized after the DRM, i.e. who have been exposed to the LDR throughout the whole treatment epoch.

In addition, analyses similar to the primary analyses will be performed on the subset of the FAS including only participants fulfilling criteria for classification for Stage 1 as defined in the draft FDA Guidance for Industry: *Early Alzheimer's disease: Developing Drugs for Treatment, February 2018.*

9.5 Analysis of secondary variables

CDR-SOB is the key secondary outcome variable. Additional secondary variables are ECog, the individual tests included in the APCC battery and RBANS, and the following AD related biomarkers: PET, Volumetric MRI, total tau and phosphorylated tau in CSF. All of the secondary endpoints will be analyzed using longitudinal models such as MMRM for the CDR-SOB similar to the approach for the primary endpoint APCC with treatment as factor and adjusting for important covariates. Hypotheses on CDR-SOB will be tested and are included in the multiple testing strategy described in Section 9.7. For CAD106, change from Month 6 to Month 60 in the APCC test score and in CDR-SOB are additional secondary outcomes and will be analyzed using the same analysis strategy as for change from baseline to Month 60.

In addition to the above listed efficacy and biomarker outcomes, the following safety and tolerability variables are secondary outcome parameters: safety MRI, AEs, laboratory tests, vital signs, and injection-related reactions for CAD106.

For CAD106, the Aβ-specific IgG response over 60 months is an additional secondary outcome.

For CNP520, the same definition of treatment arms for primary analysis will also be applied to the analysis of secondary variables.

9.5.1 Efficacy variables

Clinical Dementia Rating Scale (CDR) sum of boxes (SOB)

To control the overall type I error rate, a multiplicity adjustment will be applied to the primary and the key secondary variables, which is specified in Section 9.7.

For each of the two active investigational treatments, CAD106 and CNP520, respectively, the following null hypothesis will be tested in the framework of the multiple testing strategy:

- H_{03}: The primary active treatment arm does not differ from matching placebo in the mean change from Baseline to Month 60 in the CDR-SOB score;

The corresponding alternative hypothesis is:

- H_{13}: The primary active treatment arm differs from matching placebo in the mean change from Baseline to Month 60 in the CDR-SOB score.

The final secondary analysis of the CDR-SOB score will be performed after all participants reached 60 months of follow-up and will be performed using a longitudinal model for the change from Baseline to Month 60. A MMRM adjusted for important factors corresponding to the approach for the primary analysis model as specified for the APCC will be applied. Further specifications will be given in the statistical analysis plan (SAP).

The adjusted least square means (LSMs) for each treatment group, the difference between the LSMs (active vs placebo), the 95% confidence intervals (CIs) and the unadjusted 2-sided p-values will be calculated from the MMRM analysis and presented for each visit.

Descriptive statistics of the change from Baseline in CDR-SOB score will be presented over time by treatment group.

Sensitivity analysis of the key secondary endpoint will mirror that of the APCC primary efficacy endpoint and described more explicitly in the SAP.

Everyday Cognition scale (ECog) total score

Descriptive statistics of the change from Baseline (taken at Visit 201-Screening) in ECog total score will be presented over time by treatment group. An analysis of change from Baseline will be also performed using longitudinal MMRM model as described in Section 9.4.2.

Tests included in APCC and RBANS

Descriptive statistics of the change from Baseline in the individual test scores included in the APCC battery and RBANS, as well as the RBANS Total Scale index score, will be presented over time by treatment group. An analysis of change from Baseline will be also performed using a longitudinal MMRM model as described in Section 9.4.2.

CAD106

For Cohort I only, the change from Month 6 (when CAD106 immune response is expected to be optimal) to Month 60 in the APCC test score will be analyzed following the same strategy as for the primary analysis for the change from Baseline to Month 60.

9.5.2 Safety variables

In general, safety analyses will be carried out using the SAF. Descriptive summary tables will be provided by treatment for AEs, safety MRI and other safety parameters.

For Cohort I (CAD106 or placebo), safety parameters will also be summarized by serological responders and serological non-responders for the active CAD106 treatment arm following the concept of the MFAS. This safety analysis is meant to complement the supportive analysis of primary efficacy variables based on the MFAS and to support the interpretation of the safety analysis by comparing the safety profile between serological responders and non-responders.

AEs, SAEs and Deaths

The number (and proportion) of participants with treatment-emergent AEs (events that started after the first dose of study medication or events present prior to the start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class, and preferred term
- by treatment, primary system organ class, preferred term, and maximum severity
- by treatment, Standardized MedDRA Query (SMQ), and preferred term

Separate summaries will be provided for SAEs, death, study medication related AEs, AEs leading to discontinuation and AEs leading to dose adjustment.

Laboratory data

Summary statistics of change from Baseline laboratory results will be provided over time by treatment group. These descriptive summaries will be presented by laboratory test category, visit, and treatment group.

Shift tables based on the normal laboratory ranges will be also provided. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value is normal, low, or high for each visit relative to whether or not the Baseline value is normal, low, or high. The shift from Baseline to the most extreme post-Baseline value will also be summarized. These summaries will be presented by laboratory test category, treatment and time (if applicable).

The number and percentage of participants with clinically notable laboratory results after Baseline will be presented. The most extreme post-dose value is considered. Only participants with laboratory results at Baseline and post-Baseline from the central laboratory are included in the tabulations.

The number and percentage of participants with predefined liver enzyme abnormalities occurring during the study will be summarized by treatment group.

Vital signs

Summary statistics of change from Baseline values will be presented by vital sign parameter and treatment group. Number and percentage of participants with clinically notable vital sign changes from Baseline will be tabulated by treatment group.

Electrocardiogram (ECG)

Summary statistics of change from Baseline values will be presented by ECG parameter and treatment group. Number and percentage of participants with clinically notable ECG abnormalities will be tabulated by treatment group.

Safety brain MRI scans

Descriptive summary tables will be provided by treatment arm for safety MRI data with special focus on ARIA and white matter disease. Number, intensity and location of microhemorrhages and white matter hyperintensities using the Wahlund scale (both as assessed by central MRI reader) will be tabulated.

Potential PD-mediated DDIs with frequent concomitant medications may include the use of medications which affect the coagulation/platelet function in terms of safety (e.g. increased incidence of ARIA-H). The effect of concomitant coagulation therapy and CAD106 or CNP520 on the risk of ARIA-H will be monitored by the DMC during the study, and analyzed by anticoagulant type and by their use during the study, using the information on timing of initiation and dose as time-varying covariates in the statistical TTE models.

9.5.3 AD-related biomarkers

The following AD related biomarkers are secondary variables: amyloid and tau PET (where tracers and assessments are locally permitted i.e. not in Germany), MRI, NFL in blood/CSF, total tau and phosphorylated tau in CSF. All analyses to support secondary biomarker objectives will be performed based on the FAS.

In addition, biomarker analyses will be performed on the subset of FAS including only participants fulfilling criteria for classification for Stage 1 as defined in the draft FDA Guidance for Industry, Early Alzheimer's disease, Developing Drugs for Treatment, February 2018.

PET amyloid and tau imaging

Imaging data from amyloid and tau PET scans will be analyzed using methods previously published in the literature. The SUVR of cortical areas to the selected reference region will be used as the outcome measure.

The final secondary analysis of percent change from Baseline to Months 24 and 60 in the global cortical SUVR will be performed after all participants reached 60 months of follow-up and will be performed using a longitudinal model for percent change from Baseline: the mixed repeated measure model (MMRM).

Terms will be included for the following effects:

- treatment group
- time as the discrete variable scheduled (mapped) visit
- Baseline SUVR
- age group at baseline

and the following interaction terms

- treatment group × visit
- Baseline SUVR × visit.

The LSMs for each treatment group, the difference between the LSMs (active vs. placebo), the 95% confidence intervals, and the unadjusted 2-sided p-values will be calculated from the MMRM analysis and presented for each visit.

Summary statistics will be presented for SUVR for the global cortical amyloid load. In addition to raw values, change, and % change from Baseline will be tabulated.

Volumetric MRI

Descriptive statistics of change and relative (%) change from Baseline in volume of specific brain regions of interest (ROIs) will be presented over time by treatment group. Main ROIs include hippocampus and whole brain.

For CNP520, the following null hypotheses will be tested for specific ROIs:

- The primary active treatment arm does not differ from placebo in the mean relative change from Baseline to Month 60 in volume of the ROI as measured by volumetric MRI;

The corresponding alternative hypothesis is:

- The primary active treatment arm differs from placebo in the mean relative change from Baseline to Month 60 in volume of the ROI as measured by volumetric MRI.

The final secondary analysis of changes in volume of ROI as measured by volumetric MRI will be performed after all participants reached 60 months of follow-up and will be performed using MMRM, a longitudinal model for the change from Baseline.

Terms will be included for the following effects:

- treatment group,
- time as the discrete variable scheduled (mapped) visit,
- normalized Baseline whole brain volume,
- age group at baseline,

and the following interaction terms:

- treatment group × visit,
- normalized Baseline whole brain volume × visit.

The LSMs for each treatment group, the difference between the LSMs (active vs. placebo), the 95% confidence intervals and the unadjusted 2-sided p-values will be calculated from the MMRM analysis and presented for each visit.

Total tau and phosphorylated tau in CSF

For each of the 2 active treatments, CAD106 and CNP520, respectively, the following null hypotheses will be tested:

- The primary active treatment arm does not differ from placebo in the mean change from Baseline to Month 60 in phosphorylated tau in CSF;
- The primary active treatment arm does not differ from placebo in the mean change from Baseline to Month 60 in total tau in CSF;

The corresponding alternative hypotheses are:

- The primary active treatment arm differs from placebo in the mean change from Baseline to Month 60 in phosphorylated tau in CSF.
- The primary active treatment arm differs from placebo in the mean change from Baseline to Month 60 in total tau in CSF.

The final secondary analysis of tau in CSF score will be performed after all participants reached 60 months of follow-up and will be performed using MMRM, a longitudinal model for the change from Baseline. Terms will be included for effects of treatment group, corresponding Baseline value, scheduled (mapped) visit, and interaction terms treatment group × visit and Baseline value × visit.

The LSMs for each treatment group, the difference between the LSMs (active vs. placebo), the 95% confidence intervals and the unadjusted 2-sided p-values will be calculated from the MMRM analysis and presented for each visit.

9.5.5 Other secondary variables: Abeta-IgG response to CAD106

Immune response is measured by Aβ-specific antibody (IgG) titers in serum. Immune response will be assessed by responder rates and different summary parameters like C_{max} (peak), T_{max}, and AUC for different time intervals depending on the purpose of the analysis: Baseline to Week 26, Baseline to Month 24, Baseline to Month 60.

The serological responder definition is based on Aβ-specific antibody (IgG) titers in serum >16 units between the 2nd and the 3rd injection, AND > 3*LLOQ (LLOQ=8.93 units as determined in the phase II program, 3*LLOQ=26.8 units) after the 3rd injection. For the purposes of participant classification for the interim and final analyses, only data up to and including the Week 26 titer assessment is considered.

Non-responders will include participants who were assessed, but did not meet the criteria.

The FAS will generally be used to analyze immune response. Aβ-IgG response, responder rates, and the corresponding summary parameters (including median and inter-quartile range for the continuous response values) will be tabulated.

9.6 Interim analyses

The main purposes of the planned IAs are safety monitoring and assessment of either futility or overwhelming efficacy with the potential consequence of discontinuing the respective cohort or the whole study. Data from CCNP520A2202J study as well as knowledge from external data which is expected to become available during the course of the study will also be considered for decision making by the DMC. All IAs will be conducted by an independent DMC based on unblinded data.

Table 9-1 Schedule of pre-planned Interim analyses

	Expected timing	Main parameters under evaluation
Regular Safety Review	At least semi-annual, additional ad hoc when required	All safety data as determined by the DMC.
CNS activity futility analysis for CAD106	Once all available 24 month post-baseline data are collected for all Cohort I participants randomized up until the pause in allocation	Amyloid PET, CSF and blood parameters

	Expected timing	Main parameters under evaluation
CNS activity futility analysis for CNP520	At the latest when 24 month post-baseline CSF data are available for 270 participants across both studies API015A2201J (Cohort II) and CNP520A2202J	Volumetric MRI, CSF and blood parameters
Primary efficacy futility analysis	Once approximately 75% of the targeted number of events have occurred, but not later than 2 years prior to planned final analysis.	Primary endpoints (TTE and APCC test score)

As outlined in Table 9-1 , the Interim analyses and data review by the DMC are pre-planned for

1. Unblinded safety review by DMC:
   - Regular semi-annual and ad hoc more frequently as needed, evaluation of safety parameters, worsening in cognition as a safety measure together with data allowing risk/benefit assessment to be defined with the DMC and potential trigger for DRM in Cohort II
   - Evaluation of T-cell activation data (50 participants from Cohort I)
2. Unblinded futility Interim Analysis of immunogenicity of CAD106
3. Review of CNS activity for futility based on the following biomarkers (Refer to Section 3.1 and 3.2 for allocation pause for Cohort I):
   - CSF: Aβ (only for Cohort II (CNP520)), tau pathology (tau and p-tau)
   - Blood/CSF NFLs
   - PET imaging data: amyloid, tau, [redacted]
   - Volumetric MRI (only for Cohort II (CNP520))
4. Primary endpoint: Un-blinded analysis of primary efficacy parameters (TTE and APCC test score) to assess futility or early stopping due to overwhelming efficacy.

Interim analyses for safety

Important safety information like AEs, safety MRI data, vital signs will be regularly reported and reviewed by the DMC. The review also includes the monitoring of potential worsening in cognition based on the RBANS test score and CDR-SOB.

Interim analyses for immunogenicity of CAD106

Immunogenicity will be reviewed by the DMC following pre-specified rules: The first DMC review for the immunogenicity assessment will be scheduled at the latest after 40 participants from Cohort I (CAD106 or placebo) have received three injections and antibody titer data up to week 26 (time of 4th injection) are available.

Interim Analysis for Biomarkers of CNS activity

Cohort I

CNS activity of CAD106 will be assessed by means of a single unblinded interim analysis for participants that have had their Month 24 visit assessments. Data considered at this analysis will include %-change from Baseline in SUVR of amyloid PET at 24 months as well as all available CSF (Aβ, tau, p-tau) and volumetric MRI data (hippocampal and potentially ventricular or whole brain volume). Additional AD-related biomarkers obtained including tau PET [redacted], may also be used to further support decision making. The unblinded IA will be performed once all planned biomarker assessments have been collected for the participants randomized until the pause in Cohort I allocation.

The unblinded IA will include available 24 months data from the CAD106 treatment arm as well as both Placebo treatment arms, pooled from both cohorts.

Cohort II

CNS activity of CNP520 will be assessed by means of a single unblinded interim analysis on treatment difference from Baseline for participants that have had their month 24 visit assessments. Data considered at this analysis will include volumetric MRI data (hippocampal and potentially ventricular or whole brain volume) at 24 months as well as all available CSF data (Aβ, tau, p-tau). Additional AD related biomarkers obtained including Amyloid, Tau and [redacted]-PET, may also be used to further support decision making.

The unblinded IA will consist of a pooled analysis across studies: Cohort II of CAPI015A2201J and CCNP520A2202J, and also separated by genotype i.e., HM and non-HM. The unblinded IA will be performed at the latest when a total of approximately 270 participants across both studies in any of the CNP520 dose arms or corresponding placebo have provided CSF data at 2 years post baseline. This preliminary sample size is based on exploration of the change over 2 years from the longitudinal data from Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort data.

The exact futility decision rules for either cohort will be based on further investigation of internal and external data. Specific decision criteria and the exact timing of the analysis are under investigation and will be outlined in the DMC charter and specified in the DMC MAP.

The main purpose of these IAs is futility. No alpha spending strategy will be employed.

Primary endpoint Interim analysis

The interim analysis based on the primary endpoints (see Section 3.5) will include the testing of the following null-hypotheses:

H_{01I}: The primary active treatment arm does not differ from matching placebo with regard to the distribution of time to first diagnosis of MCI or dementia due to AD;

and

H_{02I}: The primary active treatment arm does not differ from matching placebo in the APCC time profile.

The analysis models and methods will be the same as for described in Section 9.4 for the Final Analysis. An appropriate multiplicity correction procedure will be applied for testing two endpoints at two time points, the interim and the final analysis.

The main purpose of the IA is futility. Nevertheless, since this involves unblinding of data on the primary endpoints, a small portion of the overall significance level alpha of 5% will be spent to control the type-I error rate using a Bonferroni split. The underlying idea is to set the hurdle very high such that an early stopping due to overwhelming efficacy is extremely unlikely. Early stopping rules for efficacy will refer primarily to the overwhelming efficacy on the TTE endpoint. For APCC, the rules will also take into account the status of the additional data generated to support APCC. In addition, overwhelming efficacy on APCC will need to be supported by at least a trend on TTE.

The IA will be based on available data on the two primary parameters: time to diagnosis of MCI/dementia due to AD and the APCC. The IA is planned to be conducted in each cohort as early as possible when a sufficient number of events (e.g. 75% of expected number of events) have been observed to make analysis meaningful, but the latest 2 years before the projected end of the study. It is planned to schedule the cognition IA based on a blinded review of data for the primary endpoints.

As a consequence, changes in APCC from Baseline to earlier points in time than month 60 will be investigated at the IA. The exact endpoint will depend on the amount of data available at the point in time of the cognition IA. The analysis will be based on a longitudinal MMRM model and a contrast based on time point after and including year 3. The exact hypotheses to be tested, especially for the APCC, decision rules for futility, and all other details of the cognition IA will be pre-specified and be outlined in the DMC charter and the statistical analysis plan.

9.7 Multiplicity adjustment

Cohort II

The design for Cohort II of the study has been adapted based on competitor results and new scientific evidence and literature results in 2018. The adaptation at that point was strategic and not driven by data from the ongoing studies using CNP520. The decision has been taken to allow flexibility with regards to the dose regimen. Since the decline in cognitive performance and increase in psychiatric events demonstrated in other BACE inhibitors were observed within a few months of treatment start, it is anticipated that a potential DRM would occur early in the course of the trial. As a consequence, the exposure to the initial CNP520 dose will be limited in time and short in duration compared to the overall long-term exposure to the LDR.

All proposed doses and regimens (leading to long-term BACE inhibition of at least 50%) are expected to show similar range of clinical efficacy. Potential treatment effects are expected to be driven by the long-term exposure of the final selected dose (see Section 3.3). Dose regimen modification will be driven by observation of symptomatic worsening in cognition and/or increase in neuropsychiatric events. As a consequence, it is assumed that DRM will not introduce an anticonservative bias.

Regardless of the actual dose regimen, the total sample size will remain the same, as well as the ratio of 3:2 for active:placebo. In addition, the statistical analysis will not depend on the dose

regimen, but will in any case compare active treatment (all CNP520) versus matching placebo. The primary analysis will not be adjusted for the potential DRM. Although these major design features will not change in case of DRM, it is acknowledged that the potential change in dose regimen may introduce additional variation and bias.

General

The primary analyses will consist of testing hypotheses related to the two investigational drugs, respectively. Active treatment arms will be compared vs. matching placebo. Since the placebo control includes only data from the matching placebo arms, these are considered as independent comparisons to support independent conclusion about success or failure of the trial with respect to the two investigational drugs. As a consequence, an adjustment of the type one error for the multiple testing across the two cohorts is not needed.

To ensure control of the family-wise type I error rate within cohorts, the testing of the null hypotheses on the main endpoints will be done by a gatekeeping procedure based on the graphical approach to sequential rejective multiple test procedures (Bretz et al 2009, Maurer et al 2011) that combine hierarchical and simultaneous testing based on the Bonferroni inequality.

The testing procedure is fully determined by an initial weighted graph where the elementary hypotheses are represented by vertices with associated weights representing the local significance levels. The weight associated with a directed edge between any two vertices indicates the fraction of the (local) significance level at the initial vertex (tail) that is added to the significance level at the terminal vertex (head) if the hypothesis at the tail is rejected. Together with the algorithm as specified by Bretz et al (2009) for sequentially updating the graph after rejection of a hypothesis, this approach controls the family-wise type I error rate strongly at level α.

As shown by Bretz et al (2009) the test decisions are independent of the order of rejection. If in a step of the algorithm more than one hypothesis can be rejected, the choice of the hypothesis H0i does not influence the total set of hypotheses that eventually can be rejected. The initial graph and the algorithm unequivocally define the testing strategy.

There are two primary efficacy variables and one key secondary which will be included in the multiple testing strategy. This yields to 3 statistical hypotheses which are as follows:

H_{01}: The primary active treatment arm does not differ from matching placebo with regard to the distribution of time to first diagnosis of MCI or dementia;

H_{02}: The primary active treatment arm does not differ from matching placebo in the mean change from Baseline to Month 60 in the APCC test score;

H_{03}: The primary active treatment arm does not differ from matching placebo in the mean change from Baseline to Month 60 in the CDR-SOB score;

where H_{01}, H_{02} are the primary null hypotheses, H_{03} is the key secondary null hypothesis which are included in the multiple testing strategy.

In addition to that, there are two hypotheses which will be tested at the cognition interim analysis:

H_{01I}: The primary active treatment arm does not differ from matching placebo with regard to the distribution of time to first diagnosis of MCI or dementia due to AD;

and

H_{02I}: The primary active treatment arm does not differ from matching placebo in the APCC time profile.

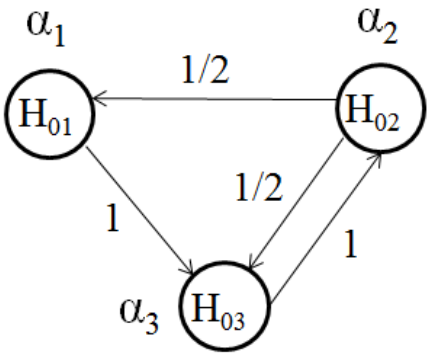
All tests will be two-sided. A small portion (a thousandth) of the overall significance level alpha of 0.05 (5%) will be spent to control the type-1 error rate across final and IA using a Bonferroni split. The two hypotheses of the cognition IA will, therefore, not be included in the graphical approach to adjust for multiplicity. An alpha of 0.00004 will be spent for testing of H_{01I} and an alpha of 0.00001 will be spent for testing of H_{02I}. Thus, an alpha of 0.04995 can be spent for testing the above specified 3 hypotheses using the graphical approach. The alpha will be split unequally (80% vs. 20%) across the two hypotheses on the two primary endpoints. Hence, an alpha of 0.03996 will be spent for testing of H_{01} and an alpha of 0.00999 will be spent for testing of H_{02}.

Significance levels $\alpha_1 = 0.03996$ and $\alpha_2 = 0.00999$ (and $\alpha_3 = 0$) are initially defined such that they sum up to $\alpha = 0.04995$.

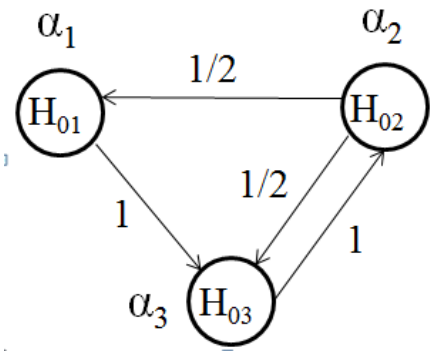
The procedure is as follows: Test the hypotheses H_{0i}, i = 1, 2, 3 each at its local significance level α_i. If a hypothesis H_{0i} can be rejected, reallocate its level to other hypotheses according to a pre-specified rule represented by an initial weighted graph. Update the reallocation weights in the reduced graph and repeat the testing step for the remaining, non-rejected hypotheses with the updated local significance levels. This possibility leads to further rejected null hypotheses with the updated local significance levels. The procedure is repeated until no further hypothesis can be rejected.

The reallocation of the local alpha levels is fully determined by the initial graph of the multiple testing strategy.

Initial graph for CAD106:



Initial graph for CNP520:



Motivation for this test procedure: These graphs are motivated by the following general considerations.

The hypotheses H_{01} and H_{02} on the primary outcomes are considered to be more important than the hypothesis H_{03} on the key secondary outcome. Thus, the significance levels are split in a way that H_{01} and H_{02} have larger initial significant levels. Once a null-hypothesis on the primary endpoints is rejected, the local initial significance level is passed on to the remaining hypothesis on the same level (primary) and/or or to the hypothesis in the lower level according to the portions specified in the graph.

Implementation of the test procedure (example):

If H_{02} is rejected, the associated level α_2 is split equally into 2 parts. One half is passed on to H_{01}, the other half is passed on to the hypothesis H_{02}. This leads to the local levels $\alpha_{1\ updated} = \alpha_1 + ½\ \alpha_2 = 0.03996 + ½ * 0.00999 = 0.04496$ and $\alpha_{3\ updated} = ½\ \alpha_2 = 0.00500$.

Table 9-2 Local levels up to second level Part I

	Local level for H_{01}	Local level for H_{03} if H_{01} rejected	Local level for H_{03} if H_{01} not rejected
H_{02} not rejected	0.03996	0.03996	0
H_{02} rejected	0.04496	0.04995	0.00500

Table 9-3 Local levels up to second level Part II

	Local level for H_{02}	Local level for H_{03} if H_{02} rejected	Local level for H_{03} if H_{02} not rejected
H_{01} not rejected	0.00999	0.00500	0
H_{01} rejected	0.00999	0.04995	0.03996

For all analyses included in the graphical approach, summary tables will present unadjusted p-values; the adjustment will be applied in the discussion of the results.

9.8 Sample size calculation

The trial will involve the assessment of efficacy for two investigational treatments. The primary analysis will compare each active investigational treatment arm to matching placebo, i.e. only the placebo arm from the same cohort will be used. For the first cohort a number of 430 participants in the active treatment arm CAD106 and 260 in the matching placebo group were calculated; for the second cohort a number of 390 in the active treatment arm CNP520 and 260 in the corresponding placebo arm. In total, 1340 participants will be randomized into the study.

Unbalanced randomization

In order to optimize recruitment, an unbalanced randomization ratio of 3:2 is selected. Slight over-allocation to CAD106 is done with a 5:3 randomization ratio to account for expected 10% of participants who will not develop serological response.

Type I error rate alpha and power

The family-wise type I error rate α will be 5% within each cohort (rate of any false positive decision, i.e. at least one Null-Hypothesis is rejected although all were true). The overall α of 5% will be split between the two primary hypotheses as follows: An alpha of 4% will be chosen to test the hypothesis H_{01} on the time to first diagnosis of MCI or dementia due to AD; an alpha of 1% will be chosen to test the hypothesis H_{02} on the APCC score. A small portion of a thousandth of the error rates will be spent (Bonferroni split) to account for multiplicity due to the IA on primary endpoints. Since the portion will be very small (Section 9.7), this has been ignored for power calculations.

Since two primary null hypotheses and one hypothesis on the key secondary endpoint will be tested simultaneously, a graphical approach (Bretz et al 2009, Maurer et al 2011) will be used to adjust for multiplicity. Tests of hypotheses will be two-sided. The details of the multiplicity adjustment and the multiple testing strategy are outlined in Section 9.7.

Sample size calculations were mainly driven by power considerations for the primary endpoint time to diagnosis of MCI due to AD or dementia due to AD, based on the variable follow-up time of 5 to approximately 8 years, with initially recruited participants followed for longer. The power, i.e. the probability to detect a true difference between treatment arms, was set to be at least 80% for this analysis.

Simulations

In addition to standard sample size calculations using the package PASS 2008, the sample size calculation of the trial has been supported by simulations. Further details are described in the Sample Size documentation.

Different sources of evidence have been used to identify reasonable assumptions for sample size calculations. Results from the literature on the lifetime risk and the risk in the age group of interest to develop AD (Jansen et al 2015, Genin et al 2011) have been used as a starting point to understand the expected event rate in the planned study population. Up to now, there are no published results available about the expected time course of the novel endpoint APCC. Hence, longitudinal data from different available cohort studies has been evaluated and used as main source of evidence to simulate trial data:

- Data from three cohort studies of aging and dementia at the Rush Alzheimer's Disease Center (the Rush Alzheimer's Disease Center's Religious Orders Study [ROS], Memory and Aging Project [MAP], or the Minority Aging Research Study [MARS]);
- longitudinal data from the National Alzheimer's Coordinating Center (NACC), Washington University which specifically included a sub-group of APOE4 homozygotes in the age range of 60-75 years.

The cohort data has been used to develop models to describe time to first diagnosis of MCI due to AD and dementia due to AD as well as for the time course of APCC. The distribution of baseline APCC, age and other characteristics from the Rush cohort have been used to simulate the target population. A number of 100 simulated trials have been used to investigate the power under different assumptions, as for instance on the age distribution. An age distribution of 1:2:2 for the age groups 60-64, 65-69, and 70-75 has been chosen which reflects the quota of 20% of participants in the lower age group. The observed event rate in 5 years in the simulated trials was about 35%-40% which is in line with the assumption on the event rate in 5 years in the target population of 25 to 35% without enrichment for older ages and up to 40% in a population with age distribution of 1:2:2 (as described above).

In Cohort II, it is assumed that all proposed active dose regimens leading to at least 50% BACE inhibition, are equally efficacious with regards to the primary clinical endpoints, and that a potential mild symptomatic worsening in cognition under active high doses of CNP520 will not impact long-term treatment effect (TTE or 5 years outcome of the APCC) of a long-term lower dose regimen not causing worsening in cognition. Hence, the following calculations apply to all potential dose regimen scenarios as described in this protocol.

Sample size calculation based on the primary endpoint time to MCI due to AD or dementia due to AD

The sample size calculation for the Time-to-event endpoint, i.e. for time to first diagnosis of MCI due to AD or dementia due to AD has been based on the following assumptions:

- 60 to 96 months observation period,
- 40% of participants experiencing an event in the control group for each cohort in 5 years observation period,
- a hazard ratio of 0.67 in favor of the active treatment group,
- 30% drop-out rate over 5 years (corresponding to a yearly drop-out rate of about 6.9%),
- $\alpha = 4\%$, two-sided test.

Power and sample size have been investigated for the comparison versus matching placebo using a Logrank test (Lakatos) with PASS 2008, a Cox PH model in simulations, and

additionally, the Schoenfeld formula (Schoenfeld 1983). Based on the above-mentioned assumptions and a randomization ratio of 3:2 (active versus placebo), a total sample size of 650 participants (390 participants in the active treatment arm and 260 in placebo) will be randomized into each cohort of the study.

Assuming a treatment effect of HR = 0.67, 218 observed events are needed to reach at least 80% power in the comparison versus matching placebo based on the Schoenfeld formula, but the power for the comparison versus matching placebo may be higher using the Cox PH model adjusting for important prognostic factors in the primary analysis. In case of an assumed HR of 0.67, the target number of events needed for each comparison of the active investigational treatment versus matching placebo is 218 for each investigational treatment. Hence, the final analysis of a cohort will be scheduled when the target number of at least 218 events has been observed within the cohort. Based on PASS 2008 and the above listed assumptions, the target number of 218 events will be observed when the last randomized participant will reach 5 years follow-up time. Assuming a smaller treatment effect of HR = 0.7, the target number of 275 events would be needed to reach at least 80% power in the comparison versus matching placebo based on the Schoenfeld formula.

Sample size and power calculations for TTE using the two-sided Logrank test (Lakatos) have been performed with PASS 2008 Version 08.0.11.

Power calculations based on the primary endpoint APCC

Power calculations for the APCC have been based on the same simulated trials as for the TTE endpoint for the comparison of each active investigational drug arm vs. matching Placebo. Hence, the above mentioned assumptions also apply to calculations for APCC. The following additional assumptions for the power calculations based on the change from baseline to Month 60 in APCC are underlying the calculations for APCC:

- Target power of 80%,
- $\alpha = 1\%$, two sided test.

The total sample size of n = 650 participants per cohort, with n = 390 participants in the active treatment arm and n = 260 in the placebo arm is sufficient to detect an effect size of 0.33 in the comparison of change from baseline to Month 60 on APCC in the active treatment arm versus matching Placebo using a simple t-test with a power of 80%. Results from simulations indicate that using a longitudinal model and adjusting for prognostic factors will increase power to detect an effect size of 0.33.

Sample size and power calculations for APCC using the two-sided t-test have been performed with nQuery Advisor 7.0.

Overall power

The overall power to detect a true treatment effect in at least one of the two endpoints on each of the investigational drugs is higher as compared to the power calculated for the single endpoints. The power increase due to testing two hypotheses depends on the relationship between the two endpoints.

On the other side, the overall power will be lower as calculated above due to multiple futility IAs. The actual loss in overall power will depend on the rules for stopping due to futility and the operating characteristics of these rules. The rules will be specified in the DMC charter and analysis plan. The operating characteristics of the rules will be assessed, and rules will be defined such that power loss will be limited.

9.9 Power for analyses of key secondary variables and target engagement of CAD106

Summary of assumptions for the power calculations based on the change from baseline to Month 60 in CDR- SOB score are the following:

- Sample size of the treatment group is 390, sample size of the control group (matching placebo) is 260
- treatment effect size of 0.33 ,
- Drop-out rate 30% over 60 months,
- Two sided two sample t-test.

The distribution of CDR-SOB and also the distribution of the change from baseline in CDR-SOB to Month 60 are expected to be right-skewed. A two-sample t-test is expected to result in more conservative power estimates in such situations as compared to other approaches such as the Mann-Whitney U test. Power calculations for the key secondary endpoint are based on the multiplicity adjustment strategy described in Section 9.7.

The different scenarios in the multiplicity adjustment strategy described in Section 9.7 will result in the appropriate relocated alpha level to be used for the power calculation for this key secondary outcome. Thereby, it is assumed that the hypothesis test statistics for the two primary null hypotheses (H_{01} for the TTE endpoint and H_{02} for the APCC score) and the key secondary null hypothesis (H_{03} for the CDR-SOB score) are independent from each other. For each of the three possible scenarios, the following power calculations were made:

1. **H_{01} is rejected, H_{02} is rejected**. The alpha levels for H_{01} and for H_{02} are both relocated for testing H_{03}, i.e. the local level for H_{03} is $\alpha_3 = 4.995\%$. The sample size of 390 vs 260 participants for active treatment vs. matching placebo group will have a conditional power of 93% to detect a clinically meaningful reduction corresponding to an effect size of 0.33 in CDR-SOB between active investigational treatment and matching placebo.
2. **H_{01} is rejected and H_{02} is not rejected**. The alpha level for H_{01} is relocated for testing H_{03}, i.e. the local level for H_{03} is $\alpha_3 = 3.996\%$. The sample size of 390 vs 260 participants for active treatment vs. matching placebo group will have a conditional power of 91% to detect a clinically meaningful reduction corresponding to an effect size of 0.33 in CDR-SOB between active investigational treatment and matching placebo.
3. **H_{01} is not rejected and H_{02} is rejected**. Half of the alpha level for H_{02} is relocated for testing H_{03}, i.e. the local level for H_{03} is $\alpha_3 = 0.5\%$. The sample size of 390 vs 260 participants for active treatment vs. matching placebo group will have a conditional power of 73% to detect a clinically meaningful reduction corresponding to an effect size of 0.33 in CDR-SOB between active investigational treatment and matching placebo.

The sample size calculations were performed using nQuery Advisor 7.0.

9.9.1 Considerations for CNS activity of CAD106

Details of the underlying assumptions and calculation of the sample size for both IAs are provided in full detail within the DMC MAP.

9.9.2 Considerations for CNS activity of CNP520

Details of the underlying assumptions and calculation of the sample size for the IA are provided in full detail within the DMC MAP.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible participants may only be included in the study after providing written IRB/IEC-approved informed consent (witnessed, where required by law or regulation), at the stages in the study where this is required. The participant should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the participant's source documents. For this study, 2 consents are required: Informed consent #1 (Part 1A is optional, Part 1B is mandatory) at start of the Pre-screening and Informed consent #2 at start of the Screening Epoch.

Novartis will provide to Investigators, in a separate document, proposed informed consent forms that comply with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to Novartis monitor after IRB/IEC approval.

The study includes optional assessments for biomarkers (PET scans, CSF and blood biomarkers) that will be captured in the main Informed consent #2 [redacted] It is required as part of this protocol that the Investigator presents all options to participants. Declining to participate in these voluntary assessments will in no way affect the participant's ability to participate in the main research study.

The study partner who will assess the participant during the study will be required to sign the informed consent as well. In case of change of person in this role during the study, the new study partner will be asked to assent by adding his/her signature next to his/her predecessor on the latest informed consent signed by the participant.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol and not under the oversight of NCRAD biobank management (see Section 6.6.3.2), additional Institutional Review Board and/or Ethics Committee approval will be obtained.

Special requirement for assessing the participant's capability to consent

Where required by the HA and/or EC/IRB, for participants who progressed to mild or early-moderate dementia* (according to investigator's judgement or confirmed by the PAC, whether dementia is due to AD or not), an additional process can be implemented to assess the participant's capacity to consent prior to the post-treatment voluntary procedures (ie. lumbar puncture and/or PET scans at Week 104 and 260). This process will involve, a qualified person who will deliver the questionnaire "Assessment of capacity to consent to the participation in the Study CAPI015A2201J" that will be included as an Appendix to the approved local version of the Informed Consent Form. Adherence to this procedure will be documented in the local study files and the completed questionnaire archived as a source document with the Informed Consent. The verbatim answers from the participant to the following questions will be captured:

1. Is your participation to the PET scans and the lumbar punctures voluntary?
2. Can you tell me why the Study Doctor wants you to undergo a PET scan of your brain during the study?
3. Can you tell me why the Study Doctor wants to take a sample of the cerebrospinal fluid during the study?
4. Which side effects could appear while cerebrospinal fluid is being taken?

The answers provided by the participant should demonstrate their capacity to understand the study requirements. The interviewer will determine the participant's capacity to consent using his/her judgment on the validity on the answers provided and may inquire further to gather additional insight when necessary.

Participants who do not demonstrate satisfactory understanding of the lumbar puncture and/or optional PET scans prior to Week 104 or 260, should not undergo these specific procedures they had consented to originally. Their study participation should nevertheless be continued if authorized by local regulations. Administration of investigational treatment, other voluntary less invasive procedures like blood sampling, and attending the protocol-specified visits can continue as planned.

* Refer to Section 5.5.9 in case of progression to late-moderate or severe dementia.

Re-consenting considerations

In case of progression to cognitive impairment, capacity to consent should be assessed by the investigator based on the changes in cognitive status that are observed, such as MCI or dementia. Participants who progress to MCI (due to AD or other causes) or dementia (due to AD) with a diagnosis confirmed by the PAC (see Section 8.5) have to confirm their consent to continue taking study treatment. In case re-consent is not obtained, they should be encouraged to still continue attending study visits as long as they agree to do so. A specific section for re-consenting to receive study treatment in such cases will be included in the ICF.

Note: Refer to Section 5.5.9 in case of progression to late-moderate or severe dementia.

Upon signs of mild cognitive impairment, the investigator may consider appropriate discussion with the participant and the study partner to notify of this decline and assess the participant willingness to continue on treatment and/or attending study visits. Loss of capacity to consent will require involvement of family or institutionally authorized representative. Such consideration will be anticipated in the ICF, with specific signature for assent from the legal representative in such case, as appropriate per local regulations (e.g. for Germany, in case of loss of capacity to consent, the participant shall be discontinued from the study).

In the event of a protocol and/or ICF amendment requiring the participant to re-consent, the investigator should use the above checklist (if applicable) and exert their judgment to assess ability to consent to the remaining study procedures and understanding any new risk information provided in the revised ICF.

10.3 Responsibilities of the Investigator and IRB/IEC

Before initiating a trial, the Investigator/institution should obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the monitors, auditors, Quality Assurance representatives, designated agents of Novartis/the CRO, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Novartis/the CRO immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

Trial data, blood, CSF, and imaging biomarker samples will also be stored for research purposes and participants will provide specific consent for such extended usage and option to share them with the scientific community under management from an independent committee.

11 Protocol adherence

This protocol defines the study objectives, the study procedures, and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances should an Investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participants included in this study even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring should be followed.

12 References

References are available upon request.

Bump in the Road or Disaster? BACE Inhibitors Worsen Cognition. AlzForum (2 Nov 2018). Retrieved from https://www.alzforum.org/news/conference-coverage/bump-road-or-disaster-bace-inhibitors-worsen-cognition

Albert MS, DeKosky ST, Dickson D, et al (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the national Institute on Aging – Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement; 7:270-9.

Bonham LW, Geier EG, Fan CC, et al (2016) Age-dependent effects of APOE e4 in preclinical Alzheimer's disease. Annals of Clinical and Translational Neurology; 3(9):668-77.

[redacted]

Bretz F, Maurer W, Brannath W, et al (2009) A graphical approach to sequentially rejective multiple test procedures. Statist. Med.; 28: 586-604.

[redacted]

Carpenter JR, Roger JH, Kenward MG, (2013) Analysis of longitudinal trials with protocol deviation: A framework for relevant, accessible assumptions and inference via multiple imputation. Journal of Biopharmaceutical Statistics; 23(6):1352-71.

[redacted]

Corder EH, Saunders AM, Strittmatter WJ, et al (1993) Gene dose of apolipoprotein E type 4 allele and the risk of alzheimer's disease in late onset families. Science; 261(5123):921-3.

Duff K, Foster NL, Dennett K, et al (2013) Amyloid Deposition and Cognition in Older Adults: The Effects of Premorbid Intellect. Arch Clin Neuropsychol. 28(7):665-71.

European Medicines Agency: Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias (2018): CPMP/EWP/553/95 Rev.2.

Egan MF, Kost J, Tariot PN, et al (2018) Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer's Disease. N Engl J Med 378:1691-703.

Farias ST, Harrell E, Neumann C, et al (2003) The relationship between neuropsychological performance and daily functioning in individuals with alzheimer's disease: ecological validity of neuropsychological tests. Archives of Clinical Neuropsychology; 18 (2003): 655-72.

Farias ST, Mungas D, Reed BR, et al (2008) The measurement of everyday cognition (ECog): Scale development and psychometric properties. Neuropsychology; 22(4):531-44.

Fine JP, Gray RT, (1999) A proportional hazards model for the sub distribution of a competing risk. Journal of the American Statistical Association; 94(446):496-509.

Folstein MF, Folstein SE, McHugh PR (1975) A practical method for grading the cognitive state of patients for the clinician. J. psychiat. Res.; 12:189-98.

Genin E, Hannequin D, Wallon D, et al (2011) APOE and Alzheimer disease: A major gene with semi-dominant inheritance. Mol Psychiatry; 16:903–07

Goos JDC, Henneman WJP, Sluimer JD, et al (2010) Incidence of cerebral microbleeds: A longitudinal study in a memory clinic population. Neurology; 74:1954-60.

Hobson VL, Hall JR, Humphreys-Clark JD, et al (2010) Identifying functional impairment with scores from the repeatable battery for the assessment of neuropsychological status (RBANS). Int J Geriatr Psychiatry.; 25(5):525-30.

[redacted]

Huang YA, Zhou B, Wernig M, et al. (2017) ApoE2, ApoE3, and ApoE4 Differentially Stimulate APP Transcription and Aβ Secretion. Cell:168(3):427-441.e21.

Jansen W, Ossenkoppele R, Knol D et al (2015) Prevalence of cerebral amyloid pathology in persons without dementia. JAMA; 313(19):1924-38.

Jonsson T, Stefansson H, Steinberg S, et al (2012) Variant of TREM2 Associated with the Risk of Alzheimer's Disease. N Engl J Med.; 368(2):107-16.

[redacted]

Karantzoulis S, Novitski J, Gold M, et al (2013) The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Utility in Detection and Characterization of Mild Cognitive Impairment due to Alzheimer's Disease. Arch Clin Neuropsychol.; 28(8):837-44.

[redacted]

Kinnecom C, Lev MH, Wendell L (2007) Course of cerebral amyloid angiopathy-related inflammation. Neurology; 68:1211-1416.

Koepsell TD, Chi YY, Zhou XH, et al (2007) An alternative method for estimating efficacy of the AN1792 vaccine for Alzheimer disease. Neurology; 69:1868-72.

Kramp VP, Herrling P (2011) List of drugs in development for neurodegenerative diseases: Update June 2010. Neurodegenerative Dis; 8:44-94.

Langbaum JB, Hendrix SB, Ayutyanont N, et al (2014) An empirically derived composite cognitive test score with improved power to track and evaluate treatments for preclinical Alzheimer's disease. Alzheimers Dement.; 10(6): 666-74.

[redacted]

[redacted]

Little RJA, and Rubin DB (2002) Statistical Analysis with Missing Data. 2nd ed; John Wiley & Sons, Inc.

Liu CC, Kanekiyo T, Xu H, et al (2013) Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat. Rev. Neurol.; 9:106-18.

[redacted]

Lo AC, Evans CD, Mancini M, et al (2018) Late Breaking News 1 : Results from the phase 2 NAVIGATE-AD clinical trial evaluating LY3202626 BACE inhibitor in patients with mild Alzheimer's Disease dementia. CTAD Barcelona 24-27 Oct 2018.

[redacted]

Lynch SY, Kaplow J, Zhao J, Dhadda, S, et al. (2018) Elenbecestat, E2609, a BACE Inhibitor: Results from a Phase-2 Study in Subjects with Mild Cognitive Impairment and Mild-to-Moderate Dementia Due to Alzheimer's Disease Abstract ID: 27524 AAIC Chicago 22-26 July 2018.

[redacted]

Maurer W, Glimm E, Bretz F (2011) Multiple and repeated testing of primary, coprimary and secondary hypotheses. Statistics in Biopharmaceutical Research; 3(2):336-352.

Mawuenyega KG, Sigurdson W, Ovod V, et al. (2010) Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science: 330(6012):1774.

McKhann GM, Knopman DS, Chertkow H, et al (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute of Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's and Dementia; 7:263-69.

[redacted]

Morris JC (1993) The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology; 43:2412-14.

Mukai Y, Mo Y, Sur C, et al (2015) Predictors of Amyloid Positivity in a Study Sample With Amnestic Mild Cognitive Impairment. Presented at CTAD.

Oh U, Gupta R, Krakauer JW, et al (2004) Reversible leukoencephalopathy associated with cerebral amyloid. Neurology; 62:494-97.

Orgogozo JM, Gilman S, Dartigues JF, et al (2003) Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization. Neurology; 61:46-54.

[redacted]

Poels MMF, Ikram MA, van der Lugt A, et al (2011) Incidence of cerebral microbleeds in the general population: The Rotterdam Scan Study. Stroke; 42:656-61.

Qian J, Wolters FJ, Beiser A, et al. (2017) APOE-related risk of mild cognitive impairment and dementia for prevention trials: An analysis of four cohorts. PLoS Med 14(3): e1002254. doi:10.1371/journal.pmed.1002254

Randolph C, (1998) The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Journal of Clinical and Experimental Neuropsychology; 20(3):310-19.

Raven JC, Court JH, Raven J (1992) Standard progressive matrices-1992 edition; Raven manual: Section 3. Oxford Psychologists Press; Oxford.

Raven JC (2000) Standard Progressive Matrices-1998 Edition, updated 2000. Manual for Standard Progressive Matrices (Section 3): NCS Person, Inc.; San Antonio.

[redacted]

Reiman EM, Chen K, Liu X, et al (2011) Fibrillar amyloid-β burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. PNAS; 106(16):6820-25.

Reiman EM, Langbaum JBS, Fleisher AS, et al (2011) Alzheimer's Prevention Initiative: A Plan to accelerate the Evaluation of Presymptomatic Treatments. Journal of Alzheimer's Disease; 26:321-29.

Rhodes J, Clay C and Phillips M (2013) The surface area of the hand and the palm for estimating percentage of total body surface area: results of a meta-analysis. B J Dermatol; 169(1):76-84.

Romano G, Raghavan N, Tymofyeyev Y, et al. (2018) Preliminary Analyses of Data from an Ongoing Trial of Atabecestat in Preclinical Alzheimer's. J Prev Alz Dis 5(S1): S44-S45.

Ropacki MT, Hannesdottir K, Hendrix S, et al (2014) Consortia driven approach to addressing clinical meaningfulness in early AD. Clinical Trial I: Trial Design and Outcome Measures; 01-05-03.

Schoenfeld DA (1983). Sample-size formula for the proportional-hazards regression model. Biometrics; 39(2): 499-503.

Sevigny J, Chiao P, Bussière T, et al (2016) The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature; 537: 50-56.

[redacted]

Sperling RA, Aisen PS, Beckett LA, et al (2011) Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimer's Dement; 7: 280–92.

[redacted]

US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (2013) Draft Guidance for Industry Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease. Docket No HFA-305. Rockville, MD.

US Department of Health and Human Services, Food and Drug Administration, Center for Biological Evaluation and research (2007) Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Docket No HFM-40. Rockville MD.

US Department of Health and Human Services, Food and Drug Administration, Draft Guidance for Industry (2018): Early Alzheimer's disease: Developing Drugs for Treatment. Docket No HFA-305. Rockville, MD.

Vassar R, Kuhn PH, Haas C, et al. (2014) Function, therapeutic potential and cell biology of BACE proteases: current status and future prospects. J. NeuroChem. P.4-28.

Vernooij MW, van der Lugt A, Ikram MA, et al (2008) Prevalence and risk factors of cerebral microbleeds: The Rotterdam Scan Study. Neurology; 70:1208-14.

Wallace AB (1951) The exposure treatment of burns. Lancet. 1(6653):501-4.

Weiss DS, et al (2004) The Impact of Event Scale-Revised. In J. P. Wilson, & T. M. Keane (Eds.), Assessing psychological trauma and PTSD: A practitioner's handbook (2nd ed., pp. 168-189). New York: Guilford Press.

Wahlund LO, Barkhof F, Fazekas F, et al (2001) A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke; 32:1318-22.