NOVARTIS

Global Clinical Development - General Medicine

CNP520

CCNP520A2202J / NCT03131453

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

Document type:	Amended Protocol Version
EUDRACT number:	2016 – 002976 - 28
Version number:	03 (Clean)
Clinical trial phase:	II/III
Release date:	7-Jan-2020

Clinical Trial Protocol Template Version 3.2 (July 2016)

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List of abbreviations

AA	Alzheimer's Association
Aβ	Amyloid-beta
ACR	Albumin Creatinine Ratio
AD	Alzheimer's Disease
ADP	Adaptation Decision Point
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	Adverse Event
AIBL	Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing
Alb	Albumin
ALP	Alkaline Phosphatse
ALT	Alanine Aminotransferase
APCC	API Preclinical Composite Cognitive Battery
API	Alzheimer's Prevention Initiative
APOE	Apolipoprotein E
AOPE4	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	German Health Authority (Bundesinstitut für Arzneimittel und Medizinprodukte)
BP	Blood Pressure
Bpm	Beats per minute
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
CHMP	Committee for Medicinal Products for Human Use
CIs	Confidence Intervals
CNAR	Censoring Not At Random
CNS	Central Nervous System
ConMed	Concomitant Medication
CPK	Creatine Phospho Kinase
CPO	Country Pharma Organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRP	C-Reactive Protein
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale

CYP3A4/2C	Cytochrome P450 3A4 / 2C
DAR	Dose Administration Record
DCF	Diagnostic Classification Form
DDI	Drug-Drug-Interaction
DMC	Data Monitoring Committee
DMI	(RBANS) Delayed Memory Index
DNA	Deoxyribonucleic Acid
DRM	Dose Regimen Modification
DTI	Diffusion Tensor Imaging
DVF	Diagnostic Verification Form
EC	Ethics Committee
ECG	Electrocardiogram
ECog	Everyday Cognition scale
eCRF	Electronic Clinical Report Form
eCSSRS	Electronic Columbia Suicide Severity Rating Scale
EDC	Electronic Data Capture
EMA	European Medicines Agency
EoS	End of Study
EoT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First-in-human
FLAIR	Fluid-Attenuated Inversion Recovery
fMRI	functional Magnetic Resonance Imaging
FWER	Family Wise type I Error Rate
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
γ-GT	Gamma Glutamyl Transferase
GRE	Gradient Echo
HA	Health Authorities
Hb	Hemoglobin
HbA1C	Glycated Hemoglobin
HDL	High Density Lipoproteins
HIV	Human Immunodeficiency Virus
HM	Homozygote for APOE-4
HMs	Homozygotes for APOE4
HT	Heterozygote for APOE-4
HTs	Heterozygotes for APOE4
IA	Interim Analysis
IN	Investigator Notification
INR	International Normalized Ratio
IB	Investigator’s Brochure
ID	Identification
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
IMI	(RBANS) Immediate Memory Index
IRB	Institutional Review Board
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
IRT	Interactive Response Technology
Kg	Kilogram
LCD	Liquid Crystal Display
LOAD	Late Onset Alzheimer's Disease
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LDR	Lower Dose Regimen
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LSM	Least Square Means
LP	Lumbar Puncture
MAP	Master Analysis Plan
MAR	Missing at Random
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
MEMS	Medication Event Monitoring System
mEoS	Modified End of Study
Mg	Milligram
mL	Milliliter
mm	Millimeter
MMRM	Mixed Model Repeated Measure
MMSE	Mini‑Mental State Examination
MNAR	Missing Not At Random
MRI	Magnetic Resonance Imaging
mTEC	Modified Treatment Epoch Completion
NACC	National Alzheimer's Co-ordination Center
NFL	Light-chain Neurofilaments
Ng	Nanogram
NIA	National Institute of Aging
NOAEL	No Observed Adverse Effect Level
NPI	Neuropsychiatric Inventory
NPI-Q	Neuropsychiatric Inventory Questionnaire
NYHA	New York Heart Association
PAC	Progression Adjudication Committee
PCR	Protein Creatinine Ratio
P-Tau	Phosphorylated-Tau
p.o.	Oral (per os)
PD	Pharmacodynamic
PET	Positron Emission Tomography
Pgp	P-Glycoproteins
PH	Proportional Hazards
PK	Pharmacokinetics
PPW	Premature Participant Withdrawal

PT-INR	Prothrombin Time-International Normalized Ratio
q.d.	Quoque die (once each day)
QOL-AD	Quality‑of‑Life in Alzheimer's disease
QM	Quality Management
QTcF	Fridericia QT correction formula
RAS	Randomized Analysis Set
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SC	Study Coordinator
sCr	serum Creatinine
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SNRIs	Serotonin Norepinephrine Re-uptake Inhibitors
SOB	Sum of Box
SOC	System Organ Class
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Re-uptake Inhibitor
STAI-AD	State Trait Anxiety Inventory for AD
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUVR	Standardized Uptake Ratio
TdP	Torsades de Pointes
TBL	Total Bilirubin
TEC	Treatment Epoch Completion
THC	Tetra-Hydro-Cannabinoid
TI	Therapeutic Index
TSH	Thyroid Stimulating Hormone
TTE	Time-To-Event
ULN	Upper Limit of Normality
USM	Urgent Safety Measure
UTE	Unsatisfactory Therapeutic Effect
VolMRI	Volumetric Magnetic Resonance Imaging
Vs	Versus
WBC	White Blood Cells
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Control drug	Drugs(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
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
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."
Medication pack number	A unique identifier on the label of each investigational drug package
Participant number	A unique number assigned to each participant upon signing the informed consent
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.
Randomization number	A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm assignment
Premature participant(s) withdrawal (PPW)	Point/time when a participant exits from the study prior to the planned completion of all investigational treatment administration and/or assessments

Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the participant as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	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
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 continue in the study any longer, and does not allow any further collection of personal data

Amendment 03 (7-Jan-2020)

Amendment rationale

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

The changes related to discontinuation of treatment with CNP520 were already formally communicated via an Urgent Safety Measure (USM) dated 11-Jul-2019 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 299 (mTEC).
    - The following assessments were no longer required: MRI, PET and Lumbar Puncture for CSF samples.
2. Modified End of Study visit 301 (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 v02 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 post-treatment assessments demonstrated reversal of the worsening in key measures of cognition after CNP520 treatment discontinuation. The unblinded 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:

This protocol amendment documents the final set of cumulative modifications after the 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: specified timing of the mEoS visit with respect to the mTEC visit
- Section 3.5 and 5.4: Additional post-treatment interim analysis after treatment termination
- Section 6: Timing of mEoS visits
- Table 6-1: Assessment Schedule for the mEoS visit 301 is modified accordingly.
- 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 5.6.5 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

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.

Summary of previous amendments

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

Amended Protocol v02 (18-Dec-2018)

Amended Protocol v01.01DE (01-Oct-2018)

Amended Protocol v01 (01-Nov-2017)

Amendment 2 (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 13Nov2018. Other changes to the protocol include change in dose adaptation strategy by introducing 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 along with a decline in cognition starting in the first 3 to 6 months of treatment. The protocol is therefore amended to include an additional cognitive assessment with RBANS at the 3 month visit, as well as the NPI-Q at 3 and 6 months and every 6 months thereafter.

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 doses of CNP520 in this study, 50 mg and 15 mg, achieve 86% and 68% median reduction of CSF Aβ, respectively.

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 incorporated into the protocol. Such dose regimen modification (DRM process) could be activated upon DMC recommendation after review of CNP520 data and/or in light of new data on either CNP520 or other BACE inhibitors. While the protocol previously included an adaptive design allowing a dose reduction from the current 50 mg to 15 mg once daily dose, this amendment removes the original adaptation process since these two doses are deemed to be too close in terms of CSF Aβ lowering and replaces it with the DRM.

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 the protocol based on Urgent Safety Measure (USM) dated 13Nov2018

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):

- Table 6-1: addition of RBANS at 3 month, NPI-Q at 3 and 6 months and every 6 months thereafter.
  Section 1 - Background: Adding results from other BACE inhibitors

Dose Regimen Modification (DRM) changes to the protocol

- Section 3.1 Addition of Dose Regimen Modification (DRM)
- Section 3.2: Addition of Dose Regimen Modification
- Section 3:3: Rationale for potential Lower Dose Regimen (LDR) if DRM is activated
- Section 3:5: Updated parameters for Interim analyses, frequency of DMC meetings and potential for DRM
- Section 5.1.1: Describing process and documentation to activate the DRM
- Section 9: Description of dose regimen and primary treatment arms for final primary analysis with or without DRM
- Section 9.4 Description of primary analysis with and without DRM
- Section 9.6 DRM added to regular DMC safety evaluation
- Section 9.7 Partial conditional error rate approach removed. Description and rationale for closed testing procedure to address situation with and without DRM added. Handling and rationale for not accounting for DRM in statistical testing approach. Discussion of potential impact of DRM on type-1 error rate
- Section 9.8 Discussion of potential impact of DRM on power and sample size
- Section 3, 9 and 17: Removed reference to the ADP, replaced by DRM adaptation of the dose regimen only
- Appendix 5: Description of partial conditional error rate approach to deal with ADP removed. Description of hypothesis with and without DRM added

Other changes to the protocol

- Section 2: Addition of exploratory analyses for APOE genotyping, brain amyloid measurements and concordance between baseline CSF and PET results for elevated amyloid criteria
- Section 4.1 and 4.2: Additional clarification for eligibility criteria
- Section 5.1.2: Defines specific radiotracers to be used in select countries
- Section 5.2: Describing process and documentation to activate the DRM.
- Section 5.4: Removes blinding instructions during ADP
- Section 5.5: Clarification of Participant numbering, Treatment assignment, dispensing and guidance dose adjustments/interruptions of study treatment
- Section 5.5.7 and 5.5.8, Table 5-1 and Table 5-2: Clarification and additional examples of restricted and prohibited treatments
- Section 5.6.3 Incorporate the new definition related to withdrawal of consent and personal data
- Table 6-1: Clarification on footnotes
  Rules for repeating MMSE during screening (at visit 101 and visit 103)
  Tau PET and LP added at PPW/TEC, relax request for amyloid PET upon PPW/EoS
  adding optional phone call for compliance check at week 6
- Table 6.2: Addition of source of genotyping, genotype result and genetic disclosure
- Section 6.1.5: Moving the Diagnostic Verification assessment of unimpaired cognition from Baseline to Screening
- Section 6.1.6.1: Description of extension of 12-week timeframe in screening period
- Section 6.1.6.2: Description on adapted screening flow for roll over participants from API015A2201J study
- Section 6.4.4.4: Local measurement of CSF cell count restricted to CNS-related safety concern in participant
- Section 6.5.2: Additional clarification on amyloid measurement method
- Section 7.2: Paper SAE reporting updated to electronic (eSAE)
- Section 7.7: clarification of use of the short eC-SSRS self-assessment PRO version
- Section 8.1: Removes the use of central analytics organization for data review
- Section 8.5: Clarifies handling and transfer of adjudication data
- Section 8.4: Ad Hoc meetings for DMC increase frequency as needed
- Section 9.4.4 Sub-group analysis 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
- Appendix 1: Provides additional guidance on ECG, liver, and renal trigger alerts
- Appendix 4: Clarifies participant referral process

- Correction to tau PET addition wording in Amendment 1 rationale: Include tau PET at screening, month 24 and month 60, to assess neurofibrillary tangles burden as a secondary endpoint (expected at the subset of sites that can access the tau tracer and have the required imaging capability)

Germany-specific local amendment 01 to protocol v01 (v01.01DE)

Amendment rationale

The current amendment to protocol version 01 addresses the changes required by BfArM dated 31 August 2018. No other changes are captured.

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 together with these Germany specific changes.

Changes to the protocol – marked as “for Germany only”

Germany specific changes according to BfArM response:

- Section 5.6.2: Adding clarification on discontinuation in case participant loses capacity to consent.
- Table 6-1: New footnote 44 for interim safety check at week 6 in Germany only
- Section 6.4.1, Section 6.4.2 and Section 7.7: Adding cross reference to Table 6-1 to clarify applicability of interim safety check at week 6.
- Section 7.7: Clarify the C-SSRS is a self-reported Web version
- Section 10.2: Specify that local regulations in Germany require the participant to be discontinued in case of loss of capacity to consent

Amendment 1

Amendment rationale

The original study protocol v00 is amended to:

Align with recent CNP520 IB update (Edition 4 released 25-Aug-2017) reflecting new data from:

- (I) GLP embryo-fetal development studies : CNP520 is not genotoxic nor teratogenic therefore male contraception is no longer required
- (II) 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. Concomitant medications associated with Torsades de Pointes are allowed, but timing of the triplicate ECGs is adjusted to expected T_{max} of CNP520
- Include tau PET at screening, 24 month and 60 month, mandatory in subset of sites to assess neurofibrillary tangles burden as a secondary endpoint (mandatory at the subset of sites that can access the tau tracer and have the required imaging capability)

Addressed the comments from the FDA on original protocol (feedback received 12-Apr-2017):

- Highlighted the rationale for a blinded dose adaptation
- Described visit window, multiplicity testing strategies and clarified timing of Interim Analyses

Incorporate additional clarifications required by investigators, health authorities and ethics committees on: Data privacy (audio-recordings, skin photographs), rater qualification, etc…

Protocol summary

Protocol number	**CCNP520A2202J**
Title	A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of CNP520 in participants at risk for the onset of clinical symptoms of Alzheimer's disease (AD).
Brief title	Study of efficacy and safety of CNP520 in comparison to 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	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine the effects of CNP520 on cognition, global clinical status, and underlying AD pathology in people at risk for the onset of clinical symptoms of AD. The study will assess progression to clinical symptoms in participants treated with CNP520 compared to placebo. This study design implements an event driven design intended to treat individual participants until the overall targeted number of events of 498 has been observed. In addition, the design takes into account the minimum treatment duration of 60 months required to assess the APCC endpoint at 5 years.
Primary Objective(s)	To demonstrate the effect of CNP520, vs placebo on time to diagnosis of MCI due to AD or dementia due to AD, whichever occurs first during the course of the study. • To demonstrate the effect of CNP520, vs placebo on cognition using API Preclinical Composite Cognitive Battery test score (APCC).
Secondary Objectives	Key secondary objective • To demonstrate the effects of CNP520 vs. placebo on global clinical status. Secondary objectives • To demonstrate the safety and tolerability of CNP520, vs placebo. • To demonstrate the effects of CNP520, vs placebo on cognition using Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). • To demonstrate the effects of CNP520, vs placebo on function. [redacted] • To demonstrate the effects of CNP520 vs placebo on brain atrophy. • To demonstrate the effects of CNP520 vs placebo on AD-related biomarkers.
Study design	The study uses a randomized, double-blind, placebo-controlled, parallel group, adaptive design with variable treatment duration in approximately 2000 cognitively unimpaired participants aged 60 to 75 years, with at least one APOE4 allele (HMs or HTs) and, if HTs, with evidence of elevated brain amyloid. The treatment duration for individual participants will be variable, based on when the end of treatment epoch criteria are met, i.e. when (1) all

	ongoing participants have completed their month 60 assessment and (2) the overall targeted number of events has been reached (see Section 3.3), whichever is later. The expected maximal duration for an individual participant is 96 months (8 years). The CNP520 50 mg dose arm is designated as the primary active arm, i.e. the active arm used for comparison with placebo in the primary analyses. The study will be conducted with a randomization ratio of 2:1:2 (CNP520 50 mg: 15 mg: placebo). This study will allow a dose regimen modification (DRM) of the CNP520 doses. Based on the Data Monitoring Committee (DMC) recommendation and/or other data from studies becoming available for CNP520 or other BACE inhibitors, either the 50 mg dose arm will be maintained as the primary active arm and the initial study design will remain unchanged, or the dose of CNP520 in both active arms will be replaced by a single lower dose regimen (LDR). The study is broadly categorized into 3 periods as Screening epoch, Treatment epoch and Follow-up epoch. **Screening** As part of informed consent process, participants will be informed of the risk of developing symptoms of Alzheimer's disease in relation to age, APOE4 genotype, and brain amyloid status. Participants may receive disclosure of their individual test results for APOE genotyping and brain amyloid status (the latter optional for HMs). Screening will include several visits, separable into two parts: screening part I and screening part II. Screening part I will include the less invasive assessments and those expected to lead to highest screen failure, i.e. participants will have their APOE genotype assessed. After genetic counseling and disclosure, participant may take a few days to reflect on this information, before continuing to screening part II. A follow up will take place two to seven days post genetic disclosure. Screening part II starts after the reflection period, and contains safety assessments, various cognitive and neuropsychological scales, brain MRI scan, and mandatory either amyloid PET scan or a lumbar puncture to verify eligibility of HTs based on brain amyloid status. Although HMs are eligible regardless of their brain amyloid elevation, they will also undergo a PET scan or a lumbar puncture during screening (HMs can opt out of amyloid disclosure). Another reflection period may take place after amyloid disclosure. A follow up will take place two to seven days post disclosure and prior to baseline (see Section 6.1). At the subset of sites, tau PET will be the last assessment prior to randomization. Altogether, the screening period from signature of ICF#B is expected to last about 12 weeks. The screening period can be extended on a case-by-case basis to accommodate scheduling. **Treatment** During the treatment period, participants who are randomized to the study will receive the investigational treatment or placebo for variable treatment duration: at least 60 months, and up to an expected maximum of 96 months. Participants will return to the study site every three months for drug dispensing. The measurements to assess efficacy endpoints are performed month 3, month 6 the first year and then every six months, and include various cognitive and neuropsychological scales with input from the study partner.

	Safety related assessments (e.g. eCSSRS, physical, skin and neurological evaluations, laboratory tests, electrocardiograms (ECGs) brain MRI scans [redacted] AD biomarkers and tau PET (at the subset of sites that can participate) are conducted according to the schedule shown in Table 6-1. Voluntary assessments include amyloid PET scans, Lumbar Puncture [redacted] **Follow-up** The Follow-up visit will be scheduled 12 weeks after the last study drug administration. Participants will undergo efficacy and safety related assessments, as described in the assessment schedule. Participants will be discharged from the study after the Follow-up visit.
Population	The study will enroll cognitively unimpaired individuals who are between the ages of 60-75 years with at least one APOE4 allele (HMs or HTs) and, if HTs, with evidence of elevated brain amyloid. Approximately 2000 participants will be randomized in approximately 180 centers worldwide.
Key Inclusion criteria (refer to Section 4.1 for exhaustive details)	**Screening part I:** Participants eligible for inclusion must fulfill all of the following criteria prior to scheduling the genetic disclosure. 1. Written informed consent must be obtained before any assessment is performed as part of the study, including consent to receive disclosure of their risk estimates to develop clinical symptoms of AD based on their APOE genotype and, if HTs, with evidence of elevated brain amyloid. 2. Male or female, age 60 to 75 years inclusive, at the time of signing the informed consent. To ensure that no more than 20% of participants in the age group 60-64 years are randomized across the whole recruitment period, a site level process will be implemented. 3. Females must be considered post-menopausal and not of child bearing potential, i.e. they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. history of vasomotor symptoms), or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation. 4. Intellectually, visually and auditorily capable, fluent in, and able to read, the language in which study assessments are administered (e.g. completion of at least six years of regular schooling or sustained employment or equivalent local level of knowledge). 5. Mini-Mental State Examination (MMSE) total score ≥ 24(can be based on documented result obtained within the previous 3 months). 6. Willing to have a study partner throughout the study. NB. Buccal swab, genetic disclosure, and corresponding 2-7 day follow-up do not need to be repeated if already performed within the API015A2201J study (roll-over participants). **Screening part II:** Participants eligible for inclusion must fulfill all of the following criteria prior to randomization based on the results from the screening test procedures. 7. Carrier of at least one ε4 allele of the APOE gene (inclusion #7a): • HMs with elevated or not elevated brain amyloid. OR

	• HTs with elevated brain amyloid (inclusion #7b) (as measured in CSF collected via lumbar puncture or by amyloid PET imaging). Note: In cases where both lumbar puncture (CSF) amyloid and amyloid PET imaging tests are performed, at least one should be indicative of elevated brain amyloid. 8. Cognitively unimpaired at screening visit as defined by : • Score of 85 or greater on the RBANS delayed memory index score AND • CDR global score of 0 with two special exceptions: – If the RBANS delayed memory index score is between 70 and 84 (inclusive) AND the global CDR = 0, the participant may be allowed to continue ONLY if the investigator judges that cognition is unimpaired following review of the MCI/dementia criteria. – If the global CDR score = 0.5 AND the RBANS delayed memory index score is 85 or greater, the participant may be allowed to continue ONLY if the investigator judges that cognition is unimpaired following review of the MCI/dementia criteria. 9. Having a study partner who agrees to participate in the study and who is intellectually, visually, and auditorily capable, and fluent in, and able to read, the language in which study assessments are administered. Additionally, the study partner must be capable of and willing to: • Accompany the participant to visits that requires the input of the study partner • Meet the definition of a “study partner” as described in Appendix 2
Key Exclusion criteria (refer to Section 4.2 for exhaustive details)	**Screening part I:** Participants will be excluded if they fulfill any of the following criteria prior to scheduling the genetic disclosure. 1. Current medical or neurological condition that might impact cognition or performance on cognitive assessments e.g., MCI , dementia, Huntington’s 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, current alcohol/drug abuse or dependence, or dependence within the last two years or history of traumatic brain injury associated with loss of consciousness and ongoing residual transient or permanent neurological signs/symptoms including cognitive deficits, and/or associated with skull fracture 2. Advanced, severe progressive or unstable disease that may interfere with the safety, tolerability and study assessments, or put the participant at special risk, e.g. active hepatitis 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), or unstable angina.

	3. History of malignancy of any organ system, treated or untreated, within the past 60 months, regardless of whether there is evidence of local recurrence or metastases. However, localized nonmalignant tumors not requiring systemic chemo- or radio-therapy, localized basal or squamous cell carcinoma of the skin, in-situ cervical cancer, localized vulvar carcinoma and localized prostate carcinoma with no progression over the past two years are permitted. 4. Current treatment with Cholinesterase Inhibitors (ChEIs) and/or another AD treatment (e.g. memantine). 5. Clinically relevant depigmenting or hypopigmenting conditions (e.g. albinism, vitiligo) or active / history of chronic urticaria in the past year. 6. Score “yes” on item four or item five of the Suicidal Ideation section of the Columbia Suicide Severity Rating Scale (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 2 years prior to screening. 7. Lacking psychological readiness to receive APOE genotype / amyloid status results, as assessed based on investigator’s judgement supported by the pre-disclosure rating scales: • Geriatric Depression Scale (GDS short form) total score > 6. • Six Item Subset Inventory of the modified State Trait Anxiety Inventory (STAI-AD) total score >17. 8. Use of other investigational drugs prior to screening until: • Small molecules: after five half-lives, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer • Biologicals: blood concentration has returned to baseline (or below serological responder threshold) for antibodies induced by active immunotherapy; or five half-lives for monoclonal antibodies or other biologicals 9. Treatment • in the four weeks prior to randomization with any drug or treatment known for the potential to cause major organ system toxicity, i.e. drugs that may require periodic safety monitoring of a specific organ or body fluid. Examples include but are not limited to clozapine, cancer medical treatment like tamoxifen, systemic immunosuppressive drugs like methotrexate or 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 drugs with the exception of those described in Table 5-2. 10. Current chronic treatment (> three months) with : • Strong CYP3A4 inducers or strong CYP3A4 inhibitor; • Drugs with a narrow therapeutic index known to be primarily metabolized by CYP2C or CYP3A isoenzymes, and sensitive P-gp substrates (.

	11. Violations of concomitant medication restrictions as described in Section 5.5.8 12. Donation or loss of 400 mL or more of blood within eight weeks prior to screening blood sampling and/or Lumbar Puncture if applicable. 13. Contraindication or intolerance to MRI investigations **Screening part II:** Participants fulfilling any of the following criteria based on results from the screening test procedures will be excluded 14. A positive drug screen, if, in the investigator's opinion, this is due to drug abuse 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. 15. Previous participation in a CNP520 study with more than three month exposure to active treatment. 16. Significantly abnormal laboratory results at screening, meeting the exclusionary alert values as described in the Appendix 1 (Table 13-3) 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. 17. Current significant ECG findings as reported by from 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 18. Brain MRI results from the central reading showing findings unrelated to AD that, in the opinion of the investigator might be a leading cause of future cognitive decline, might pose a risk to the participant, or might confound MRI assessment for safety monitoring (e.g. extensive white matter lesions, stroke, cerebrovascular disease as evidenced by multiple lacunar infarcts ≤ 20 mm or single infarct > 20 mm, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformation, subdural hematoma or space-occupying lesions). 19. **If PET scans are scheduled for this participant:** Total dosimetry above the acceptable exposure in the country when combining the previous or planned Nuclear Medicine Radiology exposure and the scheduled study PET scan(s). 20. **If CSF sampling is scheduled for this participant:** Contraindication to lumbar **puncture**, e.g. low platelet count, abnormal prothrombin time international normalized ratio (PT-INR), history of back 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.
Investigational and reference therapy	• CNP520 15 mg • CNP520 50 mg • (potential for a lower dose of CNP520 6 mg) • Arm #1: CNP520 capsule p.o. for q.d. administration at 50 mg (or LDR)

	• Arm #2: CNP520 capsule p.o. for q.d. administration at 15 mg (or LDR) • Arm #3: Placebo to CNP520 capsules p.o. for q.d. administration Both CNP520 dosage strengths will be provided as similar size and appearance (hard gelatin capsules) for oral administration (p.o.) once daily (q.d.) or once weekly (LDR) Placebo: • Matching placebo to CNP520 will be provided as capsules of similar size and appearance. Participants will be dispensed medication supplies for 3-month treatment with CNP520 50 mg or placebo for oral intake administration for the duration of the Treatment Epoch. All study treatments, including placebo, must be stored according to the storage conditions specified on the medication labels (do not store above 25°C).
Efficacy assessments	Diagnosis of MCI due to AD or dementia due to AD MMSE (included in APCC) RBANS (included in APCC) Raven's Progressive Matrices - subset (included in APCC) Clinical Dementia Rating Scale (Global score and Sum of Boxes [redacted] Everyday Cognition Scale (ECog) [redacted] volumetric brain MRI and PET scans

Safety assessments	Physical (including skin) and Neurological examination:
	• Vital signs
	• Height and Weight
	• Laboratory evaluations
	  • Hematology
	  • Clinical Chemistry
	  • Urinalysis
	• Electrocardiogram (ECG)
	• Dermatological Assessments:
	  • Skin evaluation
	  • Pruritus
	• Safety brain MRI scans
	• Adverse events (including dermatological) and serious adverse events
	• Columbia-Suicide Severity Rating Scale (eC-SSRS)

Other assessments	[redacted]
	AD Biomarkers:
	• Imaging biomarkers
	  • Volumetric MRI
	  • Diffusion tensor and diffusion weighted Imaging
	  [redacted]

	• PET scans (amyloid and tau at subset of sites)
	• Fluid biomarkers:
	  • CSF-based biomarkers (Aβ, tau, p-tau, NFLs, others)
	  • Blood-based biomarkers (serum, plasma, blood for Aβ, NFLs [redacted]

Data analysis	The final analysis will occur once the overall targeted number of events of 498 for the study has been reached and all participants have completed their month 60 assessments or PPW. 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 general, efficacy analyses will be conducted on the FAS and safety analyses on the SAF. In the situation of no DRM of CNP520 dose, the primary active arm is the 50 mg and the secondary active arm is the 15 mg. In case of DRM in both active treatment arms, the primary active arm will be defined by pooling arm #1 and #2. The primary analysis will contrast the primary active arm vs. placebo. There are two primary endpoint variables: TTE (time to first diagnosis of MCI due to AD or dementia due to AD) and the APCC test score. Success of the trial will be determined by a positive result **in at least one** primary endpoint on the primary active arm to be used for the primary analysis vs. placebo. The primary analysis to address the primary objective comprises statistical tests of hypotheses of both primary endpoints. The statistical tests will compare the primary active arm of the investigational treatment vs. placebo at the appropriate α-level. These elementary primary analyses are embedded in the overall testing procedure. To control the overall family-wise type I error rate (FWER) an appropriate multiplicity adjustment procedure using a closed testing strategy will be applied to the analyses of the primary efficacy variables. The procedure will take into account testing two endpoints, two active arms vs. placebo, and the IA on primary endpoints. For the primary active arm of the investigational drug, the following two null hypotheses will be tested corresponding to the two primary endpoints: $H_{01(1)}$: The primary active arm does not differ from placebo with regard to the distribution of time to first diagnosis of MCI due to AD or dementia due to AD; $H_{02(1)}$: The primary active arm does not differ from placebo in the mean change from baseline to month 60 in the APCC test score. The corresponding alternative hypotheses are: $H_{A1(1)}$: The primary active arm differs from placebo with regard to the distribution of time to first diagnosis of MCI due to AD or dementia due to AD; $H_{A2(1)}$: The primary active arm differs from placebo in the mean change from baseline to month 60 in the APCC test score. In a similar way, $H_{01(2)}$ and $H_{02(2)}$ and corresponding alternative hypotheses are defined for the secondary active arm. **Time-to-event** After the target overall number of events has been reached and after all participants have completed their month 60 visit or PPW, the team will

	agree on the exact cut-off date/point for the final analysis. The final TTE analysis will include data until the cut-off point in the study. Any data collected after this cut-off point will not be used for the primary analysis of TTE. That means specifically that only confirmed events collected up to the data cut-off point will be counted. Confirmation information collected after the cut-off point to confirm an earlier (meaning before the cut-off point) adjudicated diagnosis of MCI or AD due to dementia will not be taken into consideration. As a consequence, the observation will be censored at the last date prior to cut-off point that the TTE endpoint was evaluated, and the unconfirmed diagnosis will not be counted as an event in the primary analysis. The primary analysis of the TTE endpoint will be based on a Cox proportional hazards (PH) model including treatment arm as a factor and adjusted for important baseline covariates. Terms will be included for the following effects: • treatment arm • baseline value of the APCC test score • age group (60-64 years, 65-75 years) • region (North America, Europe, Asia, Other) • genotype (HM, HT). **APCC** The final primary analysis of the APCC score will use data from all participants in the FAS. The primary analysis of the APCC score will be performed using a longitudinal model for the change from baseline: the mixed model repeated measure (MMRM). An unstructured covariance matrix will be assumed, and the model will include the following baseline covariates as fixed effects: • treatment arm • time as the discrete variable scheduled (mapped) visit window • baseline value of the APCC test score • age group (60-64 years, 65-75 years) • Region (North America, Europe, Asia, Other) • Genotype (HM, HT). and the following interaction terms: • treatment arm × visit window • baseline APCC test score × visit window The adjusted least square means (LSM)s of change scores for each treatment arm, the difference between the LSMs (active vs. placebo), the 2-sided p-values (unadjusted for multiplicity) and associated confidence intervals (CIs) comparing the active and placebo LSMs, will be calculated from the MMRM analysis and presented for each visit. In addition to these primary analyses, sensitivity and supportive analyses are planned. Descriptive summary tables will be provided by treatment for AEs, safety MRI and other safety parameters based on the SAF.
Key words	Randomization, Placebo controlled, Parallel – group, APOE4 allele, homozygotes, heterozygotes, amyloid positive, preclinical Alzheimer's Disease (AD) and Aβ lowering

1 Introduction

1.1 Background

There is high unmet medical need for effective prevention and treatment of Alzheimer's disease (AD), one of the most prevalent neurological disorders among older people (i.e., >60 years of age) worldwide.

The amyloid cascade hypothesis states that deposition of amyloid-beta (Aβ) is a very early event in the pathogenesis of AD starting a decade or longer before the first clinical symptoms. Aβ aggregates in oligomers and plaques that ultimately lead to neurodegeneration and dementia of the Alzheimer type (Selkoe and Hardly 2016). Strategies that target decreasing Aβ, e.g. through inhibition of Beta-site-APP cleaving enzyme-1 (BACE-1), an enzyme involved in the processing of the amyloid precursor protein (APP), have emerged as potential disease-modifying treatments (Vassar et al 2014; Jonsson et al 2012)

The development of drugs targeting amyloid focuses increasingly on the earlier stage of AD, i.e. mild cognitive impairment (MCI) and preclinical AD, a newly defined stage of AD which reflects current evidence that measurable changes in brain biomarkers may occur years before symptoms appear (Sperling et al 2011). It is presumed that benefits of a disease-modifying therapy targeting amyloid will be greatest during these early stages. If one or more forms of Aβ play an early role in the development of AD, and if an appropriate treatment is safe, tolerated and started early enough in the disease course, this treatment could have a profound clinical and public health impact by helping to slow down or prevent the progression of AD.

The study CNP520A2202J is designed to provide efficacy, safety and tolerability data for CNP520 compared to placebo in people at risk for the onset of clinical symptoms of AD.

The Apolipoprotein E (APOE) gene is associated with Aβ clearance, aggregation, and deposition (Liu et al 2013), and carriers of the Apolipoprotein E ε4 allele (APOE4) are at greater risk for late-onset AD (Bonham et al 2016) with an increased accumulation of Aβ starting at an earlier age (Jansen et al 2015). The population for this trial will include cognitively unimpaired participants at increased risk for the onset of clinical symptoms due to AD, based on their age and APOE genotype (APOE4 homozygotes (HMs) and heterozygotes (HTs)), with the further requirement of elevated brain amyloid for HTs. Most of these participants are considered to be in a stage of preclinical AD, i.e., they are at particularly elevated risk of developing AD dementia but do not have overt symptoms and do not meet criteria for MCI or dementia (Reiman et al 2009; Sperling et al 2011).

This study will complement the ongoing CAPI015A2201J (also called "Generation Study 1") study which focuses on the APOE4 HMs population. Both studies employ the same two primary outcomes: time-to-event (TTE) with event defined as diagnosis of MCI due to AD and/or dementia due to AD), and the Alzheimer's Prevention Initiative (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 late-onset AD (Langbaum et al 2014).

CNP520

CNP520 is an orally active BACE-1 inhibitor with approximately three-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 a 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 months exposure, conducted in healthy adults ≥60 years of age. Clinical data generated to date have been collected in a total of 422 subjects that have been administered CNP520 (n = 335) or 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 APOE ε4 allele.

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 month appeared to be safe and well tolerated.

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 once a day (q.d). $A\beta_{40}$ concentrations in CSF decreased by 91% compared to baseline after three month exposure at CNP520 85 mg q.d.

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

Further details are provided in the CNP520 Investigator's Brochure (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 change in cognitive performance over the duration of the trial (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 a unique safety profile. Encouraging results obtained with elenbecestat at a dose that results in a 57% lowering of CSF Aβ 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 CNP520 on cognition, global clinical status, and underlying AD pathology in people at risk for the onset of clinical symptoms of AD. The study will assess progression to clinical symptoms in participants treated with CNP520 compared to placebo.

2 Study objectives and endpoints

Table 2-1 Objectives and related endpoints

Primary Objectives	**Endpoints**
To demonstrate the effect of CNP520 vs placebo on time to diagnosis of MCI due to AD or dementia due to AD, whichever occurs first during the course of the study.	Time to the first event with event defined as the first confirmed diagnosis of MCI due to AD or dementia due to AD.
To demonstrate the effect of CNP520 vs placebo on cognition using APCC	Change from baseline to month 60 in APCC score.
Key Secondary Objectives	
To demonstrate the effects of CNP520 vs placebo on global clinical status	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 CNP520 vs placebo	Frequencies, changes from baseline, Kaplan-Meyer estimates when applicable of : • Adverse events • Skin events based on a centralized dermatological monitoring • Safety findings from brain structural MRI central reader • Laboratory tests • Vital signs • ECG findings • Prospective suicidality assessment (ideation and behavior) from the self-reported Columbia Suicide Severity Rating Scale eC-SSRS.
To demonstrate the effects of CNP520 vs placebo on cognition using Repeatable Battery	Change from baseline to month 60 in total RBANS score and individual neurocognitive domain index scores.

for the Assessment of Neuropsychological Status (RBANS)	
To demonstrate the effects of CNP520 vs placebo on function	Change from baseline to month 60 in total score of the Everyday Cognitive (ECog) scale: ECog-subject and ECog-informant.
[redacted]	
To demonstrate the effects of CNP520 vs placebo on brain atrophy	Change from baseline to month 24 and to month 60 on volume of brain regions as measured by volumetric MRI.
To demonstrate the effects of CNP520 vs placebo on AD-related biomarkers	Change from baseline to 24 and 60 months on: • neurofibrillary tangle burden as measured by standardized uptake ratio (SUVR) of PET scans with tau tracer • amyloid deposition as measured by SUVR of tracer PET scans • CSF/blood levels of $A\beta_{40}$, $A\beta_{42}$ • neurodegeneration as measured by CSF levels of total tau and phosphorylated tau and NFL in blood/CSF Collected only in participants who consented to additional voluntary procedures

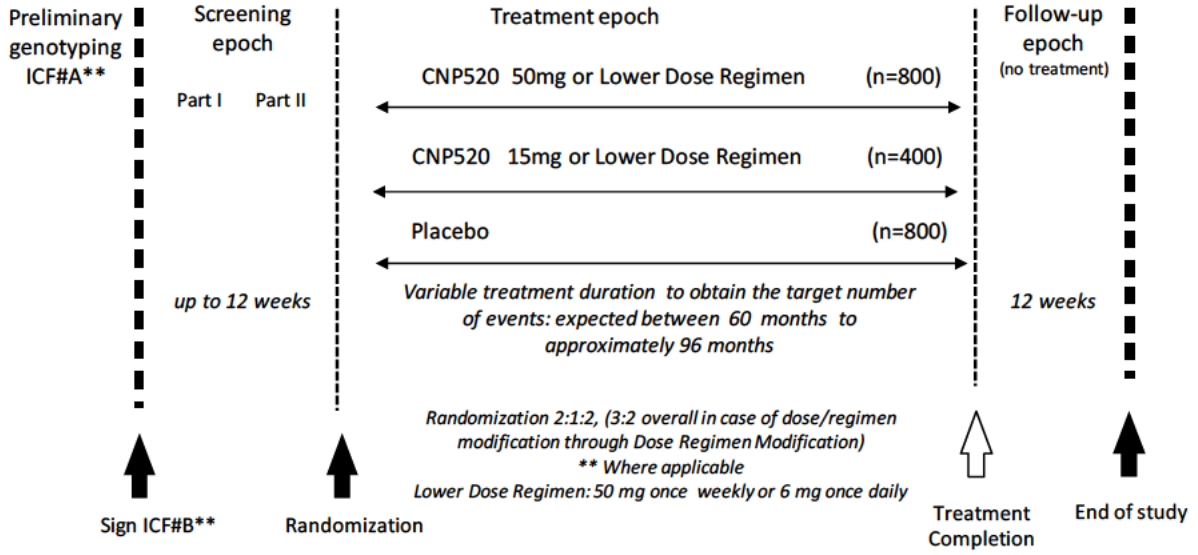
[redacted]

3 Investigational plan

3.1 Study design

The study uses a randomized, double-blind, placebo-controlled, parallel group, adaptive design with variable treatment duration in approximately 2000 cognitively unimpaired participants aged 60 to 75 years, with at least one APOE4 allele (HMs or HTs) and, if HTs, with evidence of elevated brain amyloid.

Figure 3-1 Study design



The study will be conducted with three treatment arms and randomization ratio of 2:1:2 (CNP520 50 mg: 15 mg: placebo).

The treatment duration for individual participants will be variable, based on when the end of treatment epoch criteria are met, i.e. when (1) all ongoing participants have completed their month 60 assessment and (2) the overall target number of events has been reached (see Section 3.3), whichever is later. The expected maximal duration for an individual participant is 96 months (8 years).

The initial regimen is a once daily dose of 50 mg, 15 mg, or 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 both active treatment arms through Dose Regimen Modification (DRM) process (see Section 5.1.1 and Section 5.2). This process may be triggered based on DMC recommendation and/or new data 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.

The DRM activation will follow the allocation of 2:1:2 across the three treatment arms, resulting in an overall randomization ratio of 3:2 for CNP520 (arm #1 and #2) vs placebo.

The planned total number of randomized participants will not exceed n = 2000.

Screening

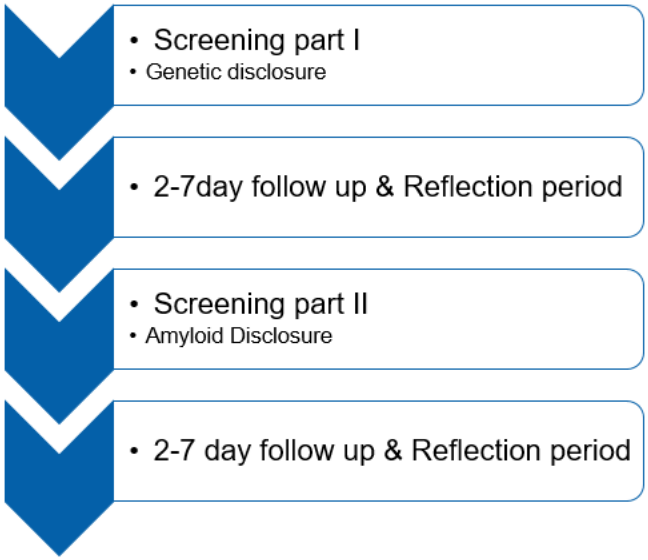
The proposed recruitment methods are described in Appendix 4. As part of the consenting process, participants will be informed of the risk estimate of developing symptoms of Alzheimer's disease in relation to age, APOE4 carriage, and brain amyloid status. As part of the Screening process (ICF#B) participants will consent to receive disclosure of their individual test results for APOE genotyping and brain amyloid status.

Screening will include several visits and will be split into two parts: screening part I and screening part II (see Figure 3-2).

A preliminary informed consent (ICF#A) may be used for APOE genotyping only, in order to enable building a local database as described in Appendix 4 scenario 4. In such cases, genotyping under ICF#A (where applicable) takes place before screening part I. Screening part I starts with ICF#B (where applicable) and will include the less invasive assessments and those expected to lead to highest screen failure. Interactive Response Technology (IRT) is contacted and participant registered as in screening after signing ICF#B. After genetic counseling and disclosure, participant may take a few days to reflect on this information before continuing to screening part II. A follow up will take place two to seven days post genetic disclosure (see Section 6.1.1 for details).

Screening part II starts after the first reflection period, and contains safety assessments, various cognitive and neuropsychological scales, brain MRI scan, and mandatory either amyloid Positron Emission Tomography (PET) scan or a lumbar puncture (LP) to verify eligibility of HTs based on brain amyloid status (see Section 6.1.4 for details and tracers). Although HMs are eligible regardless of their brain amyloid status (elevated/not elevated), they will also undergo a PET scan or a lumbar puncture during screening (HMs can opt out of amyloid disclosure). A follow up will take place two to seven days post amyloid disclosure and prior to baseline visit (see Section 6.1 for details). At the subset of sites, tau PET will be the last assessment prior to randomization. Another reflection period may take place after amyloid disclosure.

Figure 3-2 Screening parts



Altogether, the screening period (part I and part II, including reflection periods when required) is expected to last about 12 weeks. The screening period can be extended on a case-by-case basis to accommodate scheduling. In such case see Section 6.1 for guidance on assessments to be repeated to ensure continued eligibility during extended screening.

The assessments to be performed are listed in the assessment schedule (Table 6-1) and include assessments to be performed by the investigator/study site personnel, participant and study partner (see definition of study partner and role of key study site personnel in Appendix 2).

Treatment

Participants who are randomized to the study will receive the investigational treatment or placebo for variable treatment duration: at least 60 months, and up to an expected maximum of 96 months (see Section 3.3).

During the treatment period participants will return to the study site every three months for drug dispensing. The measurements to assess efficacy endpoints are performed at 3 months and 6 months during the first year and then every six months, and include various cognitive and neuropsychological scales with input from the study partner. 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 obtain by telephone interview.

Safety related assessments will include regular standard assessments (e.g. eC-SSRS, vital signs physical evaluation, laboratory tests, electrocardiograms (ECGs)), as well as specific assessments related to potential CNS or other safety assessment requirements (skin photographs and pruritus evaluation, neurological evaluations, brain MRI scans for monitoring of cerebrovascular pathology and detection of ARIA) are conducted according to the schedule shown in Table 6-1. Brain MRI scans will be read centrally at the Imaging Central Review Vendor, with safety reports provided to the Investigators and Novartis Medical Monitor. Guidance to the Investigators in case of new findings is provided in Section 13.2.

[redacted] and AD biomarkers; and tau PET scans (expected at the subset of sites that can participate) are performed according to the schedule shown in Table 6-1.

Voluntary assessments, include amyloid PET scan and/or lumbar puncture (for biomarkers [redacted]) [redacted].

At each visit, the Investigator will assess the participant for the presence of MCI or dementia using pre-specified criteria described in Section 6.3.1. 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, CNS biomarkers and clinical endpoints, throughout the study. The main purpose of the planned IAs will be safety monitoring and futility. If, at the time of the primary endpoint IA (see Section 3.5), futility is not met, the sponsor will plan an open-label extension study with CNP520 to be initiated after individual participants complete the double-blind phase of the study.

Follow-up

The Follow-up mEoS visit will be scheduled after the mTEC visit. Participants will undergo efficacy and safety related assessments, as described in the assessment schedule (Table 6-1). Participants will be discharged from the study after the Follow-up visit.

Voluntary AD-related biomarker assessments

Voluntary participation to undergo lumbar puncture for CSF collection and/or PET AD-biomarker assessments is also expected. Additional CSF collection or amyloid PET scans will be proposed to participants as follows:

- At screening: the alternative method to the one used to determine their amyloid status (CSF or PET), provided this alternative method is available.
- Post-baseline at years 2 and 5: Follow-up assessments with the method(s) used at screening.

3.2 Rationale for study design

The design of this study addresses the primary objectives, which are to assess the effect of CNP520 vs placebo on clinical progression of AD (i.e. time to diagnosis of MCI due to AD or dementia due to AD and cognition) in cognitively unimpaired participants at risk for the onset of clinical symptoms. This study design therefore implements an event driven design intended to treat individual participants until the overall targeted number of events of 498 has been observed. In addition, the design takes into account the minimum treatment duration of 60 months required to assess the APCC endpoint at the end of 5 years.

Study population

In order to select individuals with a greater likelihood of progressing to the diagnosis of MCI due to AD or dementia due to AD in a reasonable time frame, the study will enroll cognitively unimpaired individuals who are between the ages of 60 to75 years with at least one APOE4 allele (HMs or HTs) and if HTs, with evidence of elevated brain amyloid (FDA 2012 Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products; US Department of Health and Human Services, Food and Drug Administration Draft Guidance for Industry (2018), Early Alzheimer's disease, Development Drugs for Treatment on the Clinical Investigation of Medicines for the Treatment of Alzheimer's Diesease and other Dementias.

APOE4 carriers are estimated to represent about 25 to 30% of the general population and are at higher risk of developing symptoms of Late Onset Alzheimer's Disease (LOAD) than people who are non-carriers of the ε4 allele (Jansen et al 2015). The ε4 allele has been associated with reduced Aβ clearance, increased Aβ accumulation, increased Aβ-induced neurotoxicity, inflammation, reduced energy metabolism, impairment in mitochondrial function, aspects of metabolism, and other processes relevant to AD risk (Liu et al 2013). APOE4 carriers have greater fibrillar amyloid deposition than age-matched non-carriers and accelerated age-dependent cognitive decline and the amount of amyloid deposition in preclinical AD individuals and rate of cognitive decline, respectively, are directly associated with ε4 gene dose (Reiman et al 2009).

The risk of progression to MCI due to AD or dementia due to AD increases with age (Genin et al 2013). HMs are at particularly high risk (~30-55%) to develop clinical symptoms due to Alzheimer's disease by age 85 (Qian et al 2017). No further enrichment beyond genotype and age will apply to the HM population. HTs in the age range 60 to75 years have a 20-25% lifetime risk for AD by age 85. In order to identify a population with a comparable risk and a similar progression rate to HMs within the same age range, HTs will be further enriched for the presence of elevated brain amyloid at screening.

Longitudinal data from prospective cohort studies are not yet available to accurately determine risk estimates for developing dementia due to AD in cognitively unimpaired APOE4 HTs with elevated brain amyloid. However, the risk estimates were approximated based on the following:

- the estimated life-time risk by age of 85, in the HTs (~20-25%) or HMs (~30-55%) is independent of amyloid status ;
- proportion of non-elevated amyloid individuals among HTs (50%) and HMs (20%) at age of 60 to 75 years (Jansen et al 2015); and,
- the low overall risk (estimated 10%) of dementia due to AD in amyloid-negative subjects.

Using these assumptions, enrichment by elevated amyloid status increases the risk in APOE4 HTs to ~30-40%.

Design features

During the treatment duration, it is expected that at least 30% of the participants in the placebo group, either HMs or elevated amyloid HTs, will be diagnosed with MCI due to AD or dementia due to AD. The majority of the diagnoses are expected to be MCI due to AD. These assumptions of event rates are based on exploration of multiple longitudinal cohorts in observational studies. To ensure that a sufficient proportion of participants progress towards a diagnosis of MCI / dementia due to AD during the trial, the study will recruit no more than approximately 20% of participants in the age group 60-64 years. A site level process will be implemented to ensure these younger participants are enrolled throughout the recruitment period (see Section 5.5.1).

Randomization across treatment arms will be stratified by age group, genotype, method used to determined brain amyloid elevation in HT and geographic region. The method used to derive the amyloid status may result in populations with slightly different AD risk estimates. Stratification by the method will secure proper balance of treatment allocation in related subgroups. 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.

The screening assessments will be performed in sequential steps to minimize the number of participants exposed to invasive procedure (CSF sampling) or to procedures requiring transportation to other center (MRI, amyloid PET). Genotyping (APOE) and amyloid counseling and disclosure will be made available to all screened participants. The proposed flow of the screening steps is provided in Figure 6-1.

Eligibility of HTs will require confirmation of an elevated amyloid status, which can be obtained using either an amyloid PET scan **or** a lumbar puncture to measure concentration of P-tau and Aβ in CSF (see Section 6.1.4). This allows flexibility depending on medical practice (acceptability of lumbar punctures) and availability of amyloid radiotracers at the site (see Section 6.5.3.2 for allowed amyloid radiotracers).

Dose regimen modification

The study will be conducted with a randomization ratio of the original once daily regimen dose arms 50 mg: 15 mg: placebo of 2:1:2. The unequal randomization will maximize the collection of safety information on the high dose of 50 mg. Non clinical and clinical data to date suggest that both CNP520 15 mg. and 50 mg once daily doses have an acceptable safety profile. Both doses are expected to lead to CSF Aβ lowering > 50% as well as the potential LDR if activated (refer to dose rationale in Section 3.3). The CNP520 50 mg once daily dose arm is designated as the primary active arm, i.e. the active arm used for comparison with placebo in the primary analyses. Data collected for the 15 mg dose arm will then be used to increase the knowledge on safety, biomarkers, and to explore clinical efficacy of the low CNP520 dose regimen and investigate the dose-response relationship.

In case of DRM activation, the primary active arm will be defined by pooling the two active treatment arms. The primary objective of the study will compare effects of the overall long-term exposure to CNP520 through the whole study duration across the dose regimens used versus placebo.

The testing procedure will cover both cases within the same approach (see Section 9.7). The planned total number of randomized participants will be approximately 2000.

The potential bias caused by the procedure of the DRM such as potential un-blinding of investigators or participants will be operationally managed. In general, the following principles will be applied to the study to maintain the integrity and to avoid or control operational bias of any kind: (I) modification of the dose regimen is pre-planned and pre-specified in the Statistical Analysis Plan, (II) adaptation is kept to a minimum of two options for the LDR, (III) modification will be recommended by an independent DMC based on the pre-defined and specified options within the DMC charter and/or new data for CNP520 or other BACE inhibitors, (IV) the modification is restricted to the dose regimen, main design features like the total sample size, the randomization ratio, and the testing procedure remain unchanged. The DMC charter outlines the information channels for the release of DMC reviews. The amount of information about decisions following DMC recommendations to be shared with any persons involved in the study conduct will be pre-defined in the DMC charter and documented accordingly.

This design strategy allows maximizing both the potential benefit to participants as well as the amount of benefit/risk information for selection of the recommended target dose regimen of CNP520. The decision to introduce the option for DRM and to remove the original potential for adaptation 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 will be determined by a positive result in at least one endpoint.

The main primary endpoint is defined as time to first diagnosis of MCI due to AD or dementia due to AD. 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 8.5).

The alternative primary endpoint, APCC test score, will allow examination of drug effects using a continuous measure of cognition from unimpaired throughout the mild impairment stages expected to occur in the study. Although there is no currently validated cognitive test sensitive to the initial stages of impairment, the APCC test was developed based on data from multiple longitudinal observational cohorts in cognitively unimpaired individuals at baseline in the target age-range (Langbaum et al 2014). It 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 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. Individual assessments selected for inclusion in the APCC test battery are described in Section 6.3.2.

Secondary endpoints

Clinical Dementia Rating (CDR) is a global measure widely used in clinical research in AD, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is an established clinical tool used to assess the neuropsychological status, and the Everyday Cognition scale (ECog) is a measurement of daily function and evaluation of memory concerns completed by both the participant and informant. The Clinical Dementia Rating – Sum of Box (CDR-SOB) score, RBANS total score, and ECog participant/informant (i.e. study partner) scores 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 Section 6.3).

The study will also investigate the effects of CNP520 on the underlying AD pathology (e.g. amyloid and neurodegeneration: Aβtau, P-tau, NFLs in blood/CSF) assessed by additional biomarker data based on voluntary consent to lumbar punctures. 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 CNP520 to modify the course of the disease. These AD biomarker data will be also used to assess CNS activity (target engagement and downstream effects) at the CNS interim analysis (IA) (see Section 3.5).

Furthermore, biomarker data would potentially allow assessment of the effect of CNP520 vs placebo on preclinical stage 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 one), abnormal amyloid and neuronal injury markers (stage two), and abnormal amyloid and neuronal injury markers and subtle cognitive changes (stage three).

APOE4 has been linked to development of cerebral amyloid angiopathy (CAA, Greenberg et al 2014). BACE inhibitors such as CNP520 might have potential to reduce vascular amyloid load and to therefore have beneficial effects on CAA and ultimately reduce the risk for microbleeds. Appropriate monitoring with T2/fluid-attenuated inversion recovery (FLAIR) and T2* gradient echo (GRE) MRI sequences will be implemented to monitor for these events.

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

Dose

Two dose strengths of CNP520 (50 mg once daily and 15 mg once daily) are used in this study.

The targeted doses were selected based on the safety and tolerability as well as CSF Aβ lowering results obtained in the first-in-human (FIH) study CNP520X2101 and the three-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, and the 15 mg dose achieves 60% of CSF Aβ lowering in 90% of the subjects. The corresponding median CSF Aβ lowering are 86% and 68% for 50 mg and 15 mg, respectively.

Genetic data suggest that a life-long 30% reduced Aβ production 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 a greater inhibition may be required to demonstrate efficacy.

While both doses achieve a substantial effect on lowering Aβ (moderate and strong), these two doses have non-overlapping exposure distributions.

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 no-observed-adverse-effect-level (NOAEL) provide substantial coverage. The predicted safety margins Area Under Curve (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).

Overall, results from completed Phase I and Phase IIa studies indicate that both CNP520 doses of 50 mg and 15 mg p.o. daily are expected to significantly reduce Aβ levels in the CSF, with an acceptable safety and tolerability profile for long-term clinical studies. The mean terminal-half-life of approximately 150 hours in healthy elderly subjects supports once daily as well as once a week regimen.

Lower Dose Regimen (LDR)

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 50 and 15 mg once daily doses (ie. 68% and 86%, respectively) is above 60%, the original adaptation process (ADP) foreseeing a dose reduction from 50 mg to 15 mg once daily dose may not result in a sufficiently different risk/benefit ratio between the two doses. Therefore, the ADP is replaced by the option for a DRM to pre-plan for a lower dose regimen (LDR) targeting 50-60% median CSF Aβ lowering.

The independent DMC monitors the safety of CNP520 assessing regularly the unblinded data from the ongoing 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 6 mg 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 pharmacokinetics, safety and toxicity margins of the original doses and potential LDR are shown above in Table 3-1. 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, described in Table 3-1, in the study are expected to show similar range of 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 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).

Treatment duration

Based on the mechanism of action of the investigational drug, no short-term benefit is expected, particularly in the preclinical stage of AD. It is expected that if the investigational drug delays the underlying pathological or pathophysiological disease processes, these changes will emerge only gradually over time. As discussed in the CHMP Guideline (CHMP draft Guideline on the Clinical Investigation of Medicines for the Treatment of Alzheimer's Disease and other Dementias, 2018) prevention trials require long treatment durations, typically of at least five years.

In this study, participants will be treated for at least 60 months (five years) up to an expected maximum of 84 months (seven years). The minimum treatment duration of 60 months was chosen based on the likelihood of detecting (1) a 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. The expected maximum treatment duration for an individual is 96 months based on the TTE and recruitment assumptions (Section 9.8).

The relationship between the treatment duration and the overall targeted number of 498 events needed for adequate power is further explained in Section 9.8.

The process of study completion will be initiated when the overall targeted number of events for the final primary analyses is anticipated. In practice, the number of events will be monitored regularly in a blinded fashion throughout the course of the study while participants are being followed in the treatment epoch to estimate the time point when the required events (see Section 9.4.1) will occur.

The process of study completion comprises scheduling the end of treatment for each participant. At end of treatment visit Treatment Epoch Completion (TEC) or Premature Participant Withdrawal (PPW) each participant will commence the 12-week Follow-up until study completion (End of Study (EoS) visit).

The expected drop-out rate for the study is approximately 30% over 5 years, corresponding to a yearly rate of about 6.9%. While there are no similar trials recently conducted that may directly inform the design assumptions, previous studies in a more progressed population (Petersen et al 2005; Feldman et al 2007; Doody et al 2009; Doody et al 2014) and a recent meta-analysis on cardiovascular endpoint trials (across 25 trials, Rodriguez et al 2015) support this number.

3.4 Rationale for choice of comparator

Placebo will be used in a double-blind fashion. 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 or to delay onset of clinical symptoms of AD.

3.5 Purpose and timing of interim analyses/design adaptations

The main purpose of the planned Interim Analyses (IA) will be safety monitoring, dose adaptation, and assessment of either futility or overwhelming efficacy, with the potential consequence of discontinuing one active treatment arm or the whole study.

Interim analyses (also refer to Section 9.6 for details) and data review by the DMC are pre-planned as follows:

- Regular safety reviews (semi-annually, with an increased frequency as needed to appropriately evaluate the safety/tolerability profile of the current doses of CNP520 and the recommendation to maintain or modify the dose regimen via DRM):
- Safety and tolerability parameter evaluation including the assessment of potential worsening of cognition on active study drug based on selected clinical endpoints (RBANS and CDR-SOB). The initial regular safety reviews during the recruitment period will also serve the purpose of potential design adaptation..
- Two Interim analyses to assess:
  - Futility based on CNS activity using some or all of the following biomarkers:
    a. Volumetric MRI: hippocampal volume
    b. CSF: Aβ, tau, p-tau
    c. PET : tau tangles
    d. NFL in blood / CSF
  - Primary efficacy parameters (TTE and APCC test score) to assess futility or early stopping due to overwhelming efficacy.
- An additional post-treatment IA was conducted by an independent team to assess the need for continued follow-up of participants after treatment termination.

3.6 Risks and benefits

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 with 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 spontaneously. No dose-dependent AEs were identified.

In Study CCNP520X2102, with the longest exposure duration so far (i.e. three months exposure in subjects ≥60 years of age at up to 85 mg daily, with a 1-month follow-up after last dose), there was no indication for an imbalance in AE incidence between CNP520 and placebo in any of the system organ classes (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. Data from monthly dermatological assessments did not raise safety concerns. There were no clinically relevant alterations of laboratory tests, vital signs, ophthalmological assessments (visual acuity/field) or ECG data or any indication of systematic changes over time or as a function of dose.

There was also no indication of impaired neurological function during the study and after one month 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.

A pooled concentration-effect analysis of Holter- and 12-lead-ECG QT data from the first-inhuman study (CCNP520X2101), the 3-month safety and tolerability study (CCNP520X2102) and the Japanese ethnic sensitivity study (CCNP520X1101) was performed. No QTcF prolongation was observed in the pooled analysis (for further details refer to CNP520 IB).

Good Preclinical Practice (GLP) embryo-fetal development studies for CNP520 have been completed and CNP520 is not genotoxic and not teratogenic; 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 preliminary data, exposure to concomitant medications that are CYP3A4 substrates may be reduced when treatment with CNP520 is initiated. Importantly, the effect of autoinduction on systemic exposure of CNP520 is not considered to be clinically relevant since there was no decrease in exposure over three months of treatment.

No efficacy data have been generated to date. However, pharmacodynamic data have 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 tolerated (750 mg) and 95% after multiple dosing (2 weeks) at the highest dose tested (300 mg q.d.). $A\beta_{40}$ concentrations in CSF decreased by 91% compared to baseline after three 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 ε4 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 cognitive decline in pre-clinical AD stages of the disease offers potentially important benefits.

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, 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 CAPI015A2201J study) focus exclusively on APOE4 carriers who may benefit more from CNP520 based on their higher risk for amyloid accumulation leading to progression to symptomatic stages of AD. Presence of the APOE4 allele has been linked to increased amyloid-β secretion *in vitro* 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 the 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.

Risks of the procedures such as lumbar punctures, MRI and amyloid PET will be minimized by appropriate training, standardized procedures and close clinical monitoring.

The study requires participants to receive disclosure of their APOE genotype results and the corresponding risk estimates for developing AD. In addition, the individual results of amyloid status at screening (elevated / not elevated) will be communicated to APOE4 HTs. They will also be proposed to HMs (although not a criteria for eligibility, so they may choose to forgo the disclosure of the result). Individuals with high levels of emotional distress before undergoing genetic testing are more likely to have emotional difficulties after disclosure (Green et al 2009; Green et al 2014). Therefore, the study has specific criteria to exclude participants whose scores on screening assessments indicate lack of psychological readiness to receive their individual risk estimates for developing AD (based on age, APOE4 genotype and amyloid status).

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 as 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 increase in psychiatric symptoms, 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 doses do not provide an appropriate risk/benefit, they will recommend to lower the dose which is one of the criteria for activation of DRM. The recommendation from each DMC meeting is 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 v02 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

The study population will consist of cognitively unimpaired male and female participants at risk for the onset of clinical symptoms of AD, based on their age (60 to 75 years of age inclusive), APOE genotype (carrier of at least one ε4 allele) and, if HTs, evidence of elevated brain amyloid based on amyloid PET imaging or CSF testing at screening. It is expected that approximately 25-30 % of the general population without dementia are APOE4 carriers, of which about 50% are expected to have elevated brain amyloid (Jansen et al 2015) in this age group. Approximately 2000 participants will be randomized at approximately 180 centers worldwide.

4.1 Inclusion criteria

Screening part I: Participants eligible for inclusion must fulfill all of the following criteria prior to scheduling the genetic disclosure.

1. Written informed consent must be obtained before any assessment is performed as part of the study, including consent to receive disclosure of their risk estimates to develop clinical symptoms of AD based on their APOE genotype and, if HTs, their evidence of elevated brain amyloid status.
2. Male or female, age 60 to 75 years inclusive, at the time of signing the informed consent. To ensure that no more than 20% of participants in the age group 60-64 years are randomized across the whole recruitment period, a site level process will be implemented (see details in Section 5.5.1).

3. Females must be considered post-menopausal and not of child bearing potential, i.e. they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. history of vasomotor symptoms), or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation.
4. Intellectually, visually and auditorily capable, fluent in, and able to read, the language in which study assessments are administered (e.g. completion of at least six years of regular schooling or sustained employment or equivalent local level of knowledge).
5. Mini-Mental State Examination (MMSE) total score ≥ 24 (can be based on documented result obtained within the previous 3 months).
6. Willing to have a study partner (see definition Appendix 2 for definition of study partner) throughout the study.

Screening part II: Participants eligible for inclusion must fulfill all of the following criteria prior to randomization based on results from the screening test procedures

7. Carrier of at least one ε4 allele of the APOE gene (inclusion #7a):
   - HMs with elevated or not elevated brain amyloid

   OR
   - HTs with elevated brain amyloid (inclusion #7b) (as measured in CSF collected via lumbar puncture or by amyloid PET imaging).

   Note: In cases where both lumbar puncture (CSF) amyloid and amyloid PET imaging tests are performed, at least one should be indicative of elevated brain amyloid (see specific situations described in Section 6.1.4).
8. Cognitively unimpaired at screening visit as defined by:
   - Score of 85 or greater on the RBANS delayed memory index score (DMI)

   AND
   - CDR global score of 0

     with two special exceptions:
     - If the RBANS DMI score is between 70 and 84 (inclusive) AND the global CDR = 0, the participant may be allowed to continue ONLY if the investigator judges that cognition is unimpaired following review of the MCI/dementia criteria.
     - If the global CDR score = 0.5 AND the RBANS DMI score is 85 or greater, the participant may be allowed to continue ONLY if the investigator judges that cognition is unimpaired following review of the MCI/dementia criteria.
9. Having a study partner (Appendix 2) who agrees to participate in the study and who is intellectually, visually, and auditorily capable, and fluent in, and able to read, the language in which study assessments are administered.

   Additionally, the study partner must be capable of and willing to:
   - Accompany the participant to visits that requires the input of the study partner
   - Meet the definition of a “study partner” as described in Appendix 2.

4.2 Exclusion criteria

Participants fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible participants.

Screening part I: Participants will be excluded if they fulfill any of the following criteria prior to scheduling the genetic disclosure.

1. Current medical or neurological condition that might impact cognition or performance on cognitive assessments, e.g., MCI , dementia, Huntington's 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, current alcohol/drug abuse or dependence, or dependence within the last two years, or history of traumatic brain injury associated 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.
2. Advanced, severe progressive or unstable disease that may interfere with the safety, tolerability and study assessments, or put the participant at special risk, e.g. active hepatitis 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), or unstable angina.

   Note: the available Investigator Guide provides guidance on the interpretation of laboratory tests for HBV and HCV.
3. History of malignancy of any organ system, treated or untreated, within the past 60 months, regardless of whether there is evidence of local recurrence or metastases. However, localized nonmalignant tumors not requiring systemic chemo- or radio-therapy, localized basal or squamous cell carcinoma of the skin, in-situ cervical cancer, localized vulvar carcinoma and localized prostate carcinoma with no progression over the past two years are permitted.
4. Current treatment with Cholinesterase Inhibitors (ChEIs) and/or another AD treatment (e.g. memantine).
5. Clinically relevant depigmenting or hypopigmenting conditions (e.g. albinism, vitiligo) or active / history of chronic urticaria in the past year.
6. Score "yes" on item four or item five of the Suicidal Ideation section of the Columbia Suicide Severity Rating Scale (eC-SSRS patient-reported outcome), 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 2 years prior to screening.
7. Lacking psychological readiness to receive APOE genotype / amyloid status results, as assessed based on investigator's judgment supported by the pre-disclosure rating scales:
   - Geriatric Depression Scale (GDS short form) total score > 6.

- Six Item Subset Inventory of the modified State Trait Anxiety Inventory (STAI-AD) total score >17.

8. Use of other investigational drugs prior to screening until:
   - Small molecules: after five half-lives, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer
   - Biologicals: blood concentration has returned to baseline (or below serological responder threshold) for antibodies induced by active immunotherapy; or five half-lives for monoclonal antibodies or other biologicals
9. Treatment:
   - in the four weeks prior to randomization with any drug or treatment known for the potential to cause major organ system toxicity, i.e. drugs that may require periodic safety monitoring of a specific organ or body fluid. Examples include but are not limited to clozapine, cancer medical treatment like tamoxifen, systemic immunosuppressive drugs like methotrexate or 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 drugs with the exceptions of those described in Table 5-2
10. Current chronic treatment (> three months) with (see Table 5-1, expanded list is available as an Investigator Guide):
    - Strong CYP3A4 inducers or strong CYP3A4 inhibitors;
    - Drugs with a narrow therapeutic index known to be primarily metabolized by CYP2C or CYP3A isoenzymes, and sensitive P-gp substrates
11. Violations of concomitant medication restrictions as described in Section 5.5.8.
12. Donation or loss of 400 mL or more of blood within eight weeks prior to screening blood sampling and/or Lumbar Puncture if applicable
13. Contraindication or intolerance to MRI investigations.

Screening part II: Participants fulfilling any of the following criteria based on results from the screening test procedures will be excluded

14. A positive drug screen, if, in the investigator's opinion, this is due to drug abuse 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.
15. Previous participation in a CNP520 study with more than three month exposure to active treatment.
16. Significantly abnormal laboratory results at screening, meeting the exclusionary alert values as described in the Appendix 1 Table 13-2 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.
17. 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.

18. Brain MRI results from the central reading showing findings unrelated to AD that, in the opinion of the investigator might be a leading cause of future cognitive decline, might pose a risk to the participant, or might confound MRI assessment for safety monitoring (e.g. extensive white matter lesions (score of 3 on the Wahlund's scale in 2 or more bilateral brain regions), stroke, cerebrovascular disease as 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).
19. **If PET scans are scheduled for this participant:** Total dosimetry above the acceptable exposure in the country when combining the previous or planned Nuclear Medicine Radiology exposure and the scheduled study PET scan(s).
20. **If CSF sampling is scheduled for this participant:** Contraindication to lumbar puncture, e.g. low platelet count, abnormal prothrombin time international normalized ratio (PT-INR), history of back 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.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

CNP520

- CNP520 15 mg
- CNP520 50 mg

In case of DRM, new study medication and/or an 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 three treatment arms using the currently dispensed medication packs may be implemented until updated LDR medication packs are available at sites.

CNP520 dosage strengths will be provided as similar size and appearance (hard gelatin capsules) for oral administration (p.o.) in bottles supplied for at least three months of treatment.

Placebo

- Placebo to CNP520 will be provided as capsules of similar size and appearance in bottles supplied for at least three months of treatment.

An overage is included in all bottles to account for logistical constraints with visit scheduling.

All study treatments, including placebo, must be stored according to the storage conditions specified on the medication labels (do not store above 25°C) and in accordance with regulations governing investigational medicinal products and local regulations.

5.1.2 Additional treatment

If PET scans are scheduled, other study treatments include:

- an amyloid PET radiotracer: ^{18}F-florbetapir, ^{18}F-flutemetamol, or ^{18}F-florbetaben according to local regulations, (e.g. ^{18}F-florbetaben only in Germany and ^{18}F-florbetaben or ^{18}F-flutemetamol only in Canada) and,
- a tau PET radiotracer (^{18}F-flortaupicir (AV-1451), MK-6240 or PI-2620) at a subset of sites that can access a tau radiotracer and have the required imaging capability and where locally permitted (e.g. applicable for USA and Canada with ^{18}F-flortaucipir only).

It is expected that each site will use only one of the amyloid PET and one of the tau PET radiotracers. 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

Participants will be randomized at visit 201 after the pre-dose assessments have been completed. Participants will be assigned to one of the three arms with unequal randomization (2:1:2).

- Arm #1: CNP520 50 mg capsule for. p.o. administrationor CNP520 LDR if DRM is activated
- Arm #2: CNP520 15 mg capsule for p.o. administrationor CNP520 LDR if DRM is activated
- Arm #3: Placebo to CNP520 capsules for p.o. administration

If DRM is activated:

- All participants already assigned to an active treatment arm (Arm #1 or Arm #2) will be transitioned from CNP520 50 mg or 15 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 #3 will be transitioned to matching Placebo for LDR.

5.3 Treatment assignment and randomization

At baseline visit (visit 201), all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. 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 for the package(s) of study drug to be dispensed 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 study site personnel. A participant randomization list will be produced by the IRT provider using a validated system, following an automated process. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. The corresponding separate medication list(s) will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s). .

Randomization will be stratified by:

- Age: 60 to 64, 65 to 75
- Region: North America, Europe, Asia, Other
- Genotype: HM, HT
- Method used to determine amyloid status (only for HT): PET, CSF

  In case both methods were used, the one indicating elevated amyloid will be captured, and if both results indicated elevated amyloid, then PET method will be considered for stratification.

These factors will be entered by the site into the IRT at randomization call.

Rationale for stratification factors is provided in Section 3.2.

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

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 performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

1. 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:
   - [redacted]
   - DMC members and unblinded statisticians and programmers in charge of the interim DMC outputs and Interim analysis (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.

All other data with potential for unblinding (typically markers of the treatment effect) 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.

2. Although the randomization list will NOT be communicated to them, the following personnel will be considered as unblinded due to the results post-baseline:
   - AD biomarker analysts (Aβ, tau and p-tau in CSF and Aβ in plasma, NFLs in CSF/blood)
   - Analysts at the Imaging CROs (amyloid PET, tau PET)
3. The identity of CNP520 will be concealed by the use of an identical matching placebo capsule and identical packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding will only occur in the case of participant emergencies (see Section 5.5.9), and after the completion of the study.

5.5 Treating the participant

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Participant numbering

Each participant is uniquely identified in the study by a combination of center number and participant number. This is the only number assigned to the participant throughout the study. The center number (4 digits) is assigned by the sponsor to the investigative site.

Upon signing the informed consent form (ICF), the participant is assigned the next sequential 3-digit number by the investigator. At each site, the first participant is assigned participant number [redacted], and subsequent participants are assigned consecutive numbers (e.g. the second participant is assigned participant number [redacted]; the third participant is assigned participant number [redacted]). Once assigned to a participant, it will not be reused and all participants will keep the participant number from screening onwards.

If preliminary informed consent ICF#A is used, the same unique participant number will be used e.g. for buccal swab central lab requisition form. For example, if the site number is [redacted] then the participant numbers should be assigned: [redacted], etc.

Furthermore, participants who will start screening after consent under ICF#B, will keep the same participant number.

In case of re-screening a new number will be assigned sequentially by the site.

The investigator or study site personnel will contact the IRT once the participant has signed ICF#B to provide the requested identifying information for the participant to be registered. The site must select the Case Report Form (CRF) book with a matching participant number from the Electronic Data Capture (EDC) system to enter data.

IRT provides an alert at screening, to help each site to manage a ratio of maximum 20% of participants randomized in the age group 60 to 64 years. Ideally, priority should be given to

screen participants in the 65-75 age group first, and younger participants should be screened after the older ones within a group of five if possible. Otherwise, discussion with the local Novartis team is required and is documented in IRT. The same pattern will be followed for subsequent groups of participants. It is expected that "elevated amyloid levels" are less frequent in the 60-64 year age group (1 of 3 of APOE4 carriers) than in the 65-75 year age group (1 of 2 APOE4 carriers). Therefore, the rate of screen failures due to non-elevated amyloid (Inclusion #7b) will be higher in younger age group.

If the participant fails to complete the Screening epoch and is not continuing towards randomization for any reason, IRT must be notified that the participant Screen failed. The reason for Screening failure will be entered on the electronic CRF (eCRF), as well as other data listed under Section 6.2.1.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

A unique medication number is printed on each label which corresponds to one of the three 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) when they will confirm age, genotype and for HTs, the method that indicated elevated amyloid.

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 the participant has suspended study treatment, the call to IRT is still required to indicate the visit occurred but no drug was dispensed.

[redacted]

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

5.5.3 Handling of study and additional treatment

Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must 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 respective Novartis 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 study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

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

Handling of additional treatment

When PET scans are scheduled, the following non-study treatment has to be monitored specifically: amyloid PET radiotracer and tau PET radiotracer (see Section 5.1.2). Details are described in the PET procedure manual.

5.5.4 Instructions for prescribing and taking study treatment

Study medication CNP520 or placebo and an electronic cap (MEMS) will be dispensed at the baseline visit (Visit 201). Drug will then be dispensed at scheduled visits throughout the treatment epoch.

For dispensing visit days, participants must bring their bottle with the electronic cap on to the site (for drug accountability) and be instructed NOT to take the morning dose. Dosing on the site visit days will occur on site from the newly dispensed supply, after the visit assessments (especially blood sampling) are completed. Particular attention should be taken to schedule the ECGs about 2.5 hours after the drug administration (Section 6.4.5). In cases of technical hurdle (e.g. pharmacy off site drug delivery occurs in late morning) dispensing from the old bottle is allowed as long as it is documented and consistently implemented.

One capsule of CNP520 or matching placebo is to be taken orally once a day. (or once weekly if regimen changed), preferably at the same time of the day, i.e. in the morning, with or without food for approximately 60 months and up to an expected maximum of 84 months (Section 3.1). The last dose day for an individual participant will depend on when the target number of events is achieved. The last dose will be taken the day before ereatment epoch Completion (TEC) visit. The TEC will correspond to the next planned scheduled visit after information from the sponsor that target number of events has been reached.

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant and the study partner must also be instructed

to contact the investigator if the participant is unable for any reason to take the study treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Change in frequency of dosing by site or participant are not permitted. In case a daily dose was omitted, it can still be taken until approximately 6 hours after the usual once daily administration 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 one 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.

In the case that one or more dose(s) are missed, study treatment should resume as soon as possible. Any missed doses should be recorded on the Dosage Administration eCRF page. Also see Section 5.6.2 for reasons to discontinue or suspend study treatment.

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 5-1 leading to temporary suspension of investigational treatment (e.g. for an acute condition)
- develop a condition/decision leading to suspension of study treatment at any time for any reason
- who request temporary suspension of study treatment

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 (see Table 5-2).

Other CNS-active medications to control behavioral changes are allowed with restrictions as specified in Table 5-2.

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

5.5.7 Concomitant medication

The investigator must instruct the participant 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 was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started.

Treatment for pruritus

In case of occurrence of pruritus, additional investigations and treatment should be performed as per local standard of practice. Treatment may include liberal uses of local emollients or oral anti-histamines. No other specific active treatment is recommended in the absence of inflammation/rash. If the pruritus is accompanied by an associated skin lesion/rash, a photograph will be taken for centralized dermatological assessment and topical steroids may be used. Systemic steroids should be reserved for cases of severe rash or other associated systemic symptoms. For moderate or severe pruritus referral to a specialist is recommended.

For further information in relation to skin reaction and or pruritus, refer to Section 6.4.6.2.

5.5.8 Prohibited medication

Use of the treatments listed in Table 5-1 is NOT allowed after the start of investigational drug.

Treatment with any drug or treatment known for its potential to cause major organ system toxicity, i.e. drugs that may require periodic safety monitoring of a specific organ or body fluid.

- Chronic use (> three months) of (extensive list of the drugs covered below is available as an Investigator Guide):
  - 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 P-gp substrates are prohibited, since CNP520 may be a weak inducer of CYP3A4 and consequently potentially also of CYP2C9 and P-Glycoproteins (P-gp).
- In addition, CNS-active drugs are generally prohibited except if listed and used within the restricted conditions specified in Table 5-2.

Table 5-1 Prohibited medication

Medication	Prohibition period	Action taken during treatment phase
Any drug or treatment known for its potential to cause major organ	Pre-dose see Exclusion criteria #9	Any use: Discontinue investigational treatment,

Medication	Prohibition period	Action taken during treatment phase
system toxicity, i.e. drugs that require safety 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 immunosuppressive biological medicines for rheumatic diseases or multiple sclerosis	Whole study duration (Treatment and Follow-up epochs)	continue monitoring participant at scheduled study visits until PPW or EoS
Strong CYP3A inducer (e. g. carbamazepine , phenytoin, rifampicin , St John's wort)	Pre-dose see Exclusion criteria #10 Whole study duration (Treatment and Follow-up epochs)	**Acute use:** allowed, no action (continue study treatment and visits) **Chronic use** (> three months): Discontinue investigational treatment, continue monitoring participant at scheduled study visits until Premature Participant Withdrawal (PPW) or End of Study (EoS)
Strong CYP3A inhibitor (e.g. clarithromycin, grapefruit juice, itraconazole)	Pre-dose see Exclusion criteria #10 Whole study duration (Treatment and Follow-up epochs)	**Acute use:** Suspend investigational treatment; continue monitoring the participant at scheduled study visits, resume investigational treatment upon discontinuation of the strong CYP3A4 inhibitor **Chronic use** (> three months): Discontinue investigational treatment, continue monitoring participant at scheduled study visits until Premature Participant Withdrawal (PPW) or End of Study (EoS)
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 (digoxin, talinolol).	Pre-dose see Exclusion criteria #10 Whole study duration (Treatment and Follow-up epochs)	**Acute use:** Suspend investigational treatment; continue monitoring the participant at scheduled study visits, resume investigational treatment upon discontinuation of the drug with narrow TI. **Chronic use:** 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	Pre-dose see Exclusion criteria # 9 Whole study duration (Treatment and Follow-up epochs)	**Acute use:** Suspend investigational treatment; continue monitoring the participant at scheduled study visits, resume investigational

Medication	Prohibition period	Action taken during treatment phase
otherwise specified in Table 5-2 below		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

Table 5-2 Restricted treatments

Medication	Restrictions / action to be taken during treatment phase
Anti-coagulants	Anti-coagulant treatments are allowed. However, when appropriate, review the International normalized ratio (INR) level and adjust dosage according to the prescribing information.
CNS active drug: Cholinesterase inhibitor or memantine (permitted only after diagnosis of dementia due to AD and not during the preclinical or MCI stage).	If initiated during the study (see Section 5.5.6) , maintain a stable dose in the six weeks prior to clinical evaluations
CNS active drug: 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 administration 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). 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 or fMRI (as applicable).
CNS active drug: 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).

Medication	Restrictions / action to be taken during treatment phase
CNS active drug: 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 administration 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). Resting state fMRI need not be performed during MRI examinations.
CNS active drug: 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 six weeks prior to clinical evaluation.
CNS active drug: Chronic or acute 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 that 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 Emergency breaking of assigned treatment code

In general, circumstances that might lead to emergency breaking of an assigned treatment code are uncommon. One unusual circumstance in which the breaking of an assigned treatment code might be necessary is when a participant requires emergency surgery and the anesthesiologist needs to know all medications to which the participant has been exposed in order to make proper decisions about treatment and support during the surgery.

Emergency code breaks must only be undertaken when it is required in order to treat the participant safely. Most often, study 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 Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

In case of emergency code breaking, the participant can continue attending the study visits and perform the protocol-required assessments until EoS but he/she cannot resume study treatment. If an extension is implemented, he/she may be eligible after a full assessment has been performed, condition has resolved and causality to study drug ruled out by the investigator or the DMC.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

The study will be considered completed when all the following conditions are met:

1. Target number of events has been reached
2. All individual participants have performed their scheduled month 60 or the PPW visit
3. All participants have completed their Follow-up visit

Assuming the Target number of events was reached, the Treatment Epoch will complete 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 PPW/TEC column will be completed unless they were performed in the timeframe specified in footnote 37 to Table 6-1.

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

5.6.2 Discontinuation of study treatment

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

Participants who progress to MCI/dementia due to AD should continue on the 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 Informed Consent (participant wish, see Section 5.6.3)
- In the unlikely event of Pregnancy (see Section 7.6)
- Use of prohibited treatment leading to discontinuation of treatment as per Table 5-1 or meeting criteria for treatment discontinuation with restricted medications listed in Table 5-2
- Any other protocol deviation or situation that results in a significant risk to the participant's safety
- Meeting the criteria for discontinuing the investigational treatment due to:
  - 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, laboratory tests, vital signs or ECG (Appendix 1).

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 5-1 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 they explicitly withdraw their consent. They are expected to continue attending study visits according to protocol assessments as planned in the assessment schedule (with exception of drug dispensing and drug administration). 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 5.6.4.

Missed or rescheduled visits or assessments should not lead to automatic discontinuation.

Assessments required upon discontinuation from treatment epoch are detailed in the "PPW" column in the assessment schedule (Table 6-1) should be completed and recorded in the eCRF. The investigator must determine the primary reason for the participant's discontinuation of study treatment and record this information on the Dosage Administration eCRF.

Participants must be followed for 12 weeks after their last administration 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 assessments (EoS).

The investigator must also contact the IRT to register the participant's discontinuation from study treatment, and also register the visits with no treatment dispensed until PPW/TEC and EoS.

5.6.3 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore

and

- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand 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.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the participant's study withdrawal should be made as detailed in the assessment Table 6-1, PPW visit.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a participant's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

5.6.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant cannot be considered as lost to follow-up until the time point of his/her scheduled EoS visit has passed.

5.6.5 Early study termination by the sponsor

Novartis may terminate the trial for reasons related to the benefit/risk assessment of treatment for participants in the study, or for regulatory or medical reasons (including slow enrollment) in consultation with the DMC. In the event that the study is terminated early, the HAs and IRBs/ECs will be informed on reasons for early termination and the process to prematurely withdraw the participants. 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

A preliminary step may be performed to obtain a buccal swab for APOE genotyping to be recorded in the local site database using the dedicated ICF#A. (refer to Appendix 4)

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Participants must be seen for all visits during the designated period, or as close to it as possible. Scheduled study visits during the treatment epoch may require multiple visits spread over different days that should be scheduled within the ±4-week window (exception for the cognitive assessments at month 3 [redacted], see Table 6-1, footnote 45). Missed or rescheduled visits or assessments should not lead to automatic discontinuation. Upon study drug discontinuation, all dispensed investigational product should be reconciled.

Participants are encouraged to continue attending study visits even after study drug discontinuation. After the Early Termination of the treatment per the 11 July 2019 USM notification, mEoS 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.

All adverse events and concomitant medications should be reconciled on the eCRF prior to End of Study (EoS).

Table 6-1 Assessment schedule

Epoch	Screening[2]							Treatment												
Visit Name	Scr1	Scr2	Scr3	Scr4	Scr5	Scr6	Scr7	Bas	Y1Q1[39]	Y1Q2	Y1Q3	Y1Q4	Y2Q1	Y2Q2	Y2Q3	Y2Q4	Y3Q1	Y3Q2	Y3Q3	Y3Q4
Visit Numbers	101	102	103	104	105	106	107	201	202	203	204	205	206	207	208	209[40]	210	211	212	213
Weeks									13	26	39	52	65	78	91	104	117	130	143	156
Main study Informed consent (ICF#B)	X[3,4]																			
Inclusion / Exclusion criteria	S		S[5]					S[5]												
Medical history/current meds/AD family history	X																			
APOE Genotype (buccal swab) may be done as a preliminary step using ICF#A	X[6]																			
Vital Signs[7]	X							X(S[44])	X	X	X	X		X		X		X		X
MMSE	X[8]		X[8]					X[9]		X		X		X		X		X		X
[redacted]																				
Electrocardiogram (ECG)[15]		X[14]							X	X		X		X		X		X		X
Physical / Skin / Neurological Exam		S						(S[44])	S[16]	S[16]		S[16]		S[16]		S[16]		S[16]		S[16]
[redacted]																				
MCI / Dementia Diagnostic Verification[18]/ Classification			X [33]							X		X		X		X		X		X
RBANS (APCC)[19,20]			X					X[9]	X[9,45]	X		X		X		X		X		X
Raven's (APCC)[19,20]			X					X		X		X		X		X		X		X

Epoch	Screening[2]							Treatment												
Visit Name	**Scr1**	**Scr2**	**Scr3**	**Scr4**	**Scr5**	**Scr6**	**Scr7**	**Bas**	**Y1Q1[39]**	**Y1Q2**	**Y1Q3**	**Y1Q4**	**Y2Q1**	**Y2Q2**	**Y2Q3**	**Y2Q4**	**Y3Q1**	**Y3Q2**	**Y3Q3**	**Y3Q4**
Visit Numbers	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**209[40]**	**210**	**211**	**212**	**213**
Weeks									**13**	**26**	**39**	**52**	**65**	**78**	**91**	**104**	**117**	**130**	**143**	**156**
CDR, ECog[19,21,20,18]			X							X		X		X		X		X		X
[redacted]																				
[redacted]																				
MRI (safety, volMRI, [redacted])[22,20]				X[23]						X		X				X				X
Amyloid PET[22,20]					X[11,23,24]											X[25]				
Tau PET[26]							X[27]									X				
Drug Dispensing and Administration[28]								X[29]	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																				
AE/SAE/ConMeds	As needed																			
eC-SSRS	X		X[10]				X[10]	Every visit including unscheduled visits ([44])												
Laboratory evaluations		X[14,34]							X	X		X		X		X		X		X
[redacted]																				
Lumbar puncture[22,35,36,25]					X[24,23]											X[25]				
[redacted]																				
Biomarker Plasma/Serum					X				X	X		X				X				X

Epoch	Treatment																			
Visit Name	**Y4Q1**	**Y4Q2**	**Y4Q3**	**Y4Q4**	**Y5Q1**	**Y5Q2**	**Y5Q3**	**Y5Q4**	**Y6Q1**	**Y6Q2**	**Y6Q3**	**Y6Q4**	**Y7Q1**	**Y7Q2**	**Y7Q3**	**Y7Q4**	**Y8Q1**	**Y8Q2**	**Y8Q3**	**PPW/TEC**
Visit Numbers	**214**	**215**	**216**	**217**	**218**	**219**	**220**	**221[40]**	**222[41]**	**223[41]**	**224[41]**	**225[41]**	**226[41]**	**227[41]**	**228[41]**	**229[41]**	**230[41]**	**231[41]**	**232[41]**	**299[42]**
Weeks	**169**	**182**	**195**	**208**	**221**	**234**	**247**	**260**	**273**	**286**	**299**	**312**	**325**	**338**	**351**	**364**	**377**	**390**	**403**	**415**
Vital Signs[7]		X		X		X		X		X		X		X		X		X		X
MMSE		X		X		X		X		X		X		X		X		X		X
[redacted]																				
Electrocardiogram (ECG)		X		X		X		X		X		X		X		X		X		X
Physical / Skin / Neurological Exam		S[16]		S[16]		S[16]		S[16]		S[16]		S[16]		S[16]		S[16]		S[16]		S[16]
[redacted]																				
MCI / Dementia Diagnostic Classificaton[18]		X		X		X		X		X		X		X		X		X		X
RBANS (APCC), Raven's (APCC)[19,20]		X		X		X		X		X		X		X		X		X		X
CDR, ECog[19,21,20,18]		X		X		X		X		X		X		X		X		X		X
[redacted]																				
MRI (safety, volMRI, [redacted])[22,20]				X				X				X				X				X[37]
Amyloid PET[22,20]								X[25]												X[25, 37]
Tau PET[26]								X												X[37]
Drug Dispensing and Administration[28]	X	X	X	X	X	X	X	X	X[38]	X[38]	X[38]	X[38]	X[38]	X[38]	X[38]	X[38]	X[38]	X[38]	X[38]	
[redacted]																				
AE/SAE/ConMeds	As needed																			
eC-SSRS	Every visit including unscheduled visits																			
Laboratory evaluations		X		X		X		X		X		X		X		X		X		X
[redacted]																				

Epoch	Treatment																			
Visit Name	**Y4Q1**	**Y4Q2**	**Y4Q3**	**Y4Q4**	**Y5Q1**	**Y5Q2**	**Y5Q3**	**Y5Q4**	**Y6Q1**	**Y6Q2**	**Y6Q3**	**Y6Q4**	**Y7Q1**	**Y7Q2**	**Y7Q3**	**Y7Q4**	**Y8Q1**	**Y8Q2**	**Y8Q3**	**PPW/TEC**
Visit Numbers	**214**	**215**	**216**	**217**	**218**	**219**	**220**	**221[40]**	**222[41]**	**223[41]**	**224[41]**	**225[41]**	**226[41]**	**227[41]**	**228[41]**	**229[41]**	**230[41]**	**231[41]**	**232[41]**	**299[42]**
Weeks	**169**	**182**	**195**	**208**	**221**	**234**	**247**	**260**	**273**	**286**	**299**	**312**	**325**	**338**	**351**	**364**	**377**	**390**	**403**	**415**
Lumbar puncture[22,35,36,25]								X[25]												X[25, 37]
[redacted]																				
Biomarker Plasma/Serum				X				X				X				X				X[37]

Epoch	Follow up
Visit Name	mEoS
Visit Numbers	301[43]
Body Weight	X (only if on-site visit)
AE/SAE/ConMeds	X
eC-SSRS	X (only if on-site visit)

APCC = API Preclinical composite cognitive; CDR = Clinical dementia rating; Cdns: Conditions; C-SSRS = Columbia Suicide Severity Rating Scale; DMI: (RBANS) Delayed Memory Index; DVF : Diagnostic Verification Form; DCF: Diagnostic Classification Form; Drug Disp & Admin: Drug Dispensing & Administration; ECog = Everyday Cognition scale participant reported outcome; f : functional; [redacted]; LP: Lumbar Puncture MCI = Mild cognitive impairment; MMSE = Mini-Mental State Examination; MRI = Magnetic resonance imaging; Neurol : Neurological; [redacted]; PET = Positron emission tomography; PPW = Premature Participant Withdrawal; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; S = Source data; TEC = Treatment Epoch Completion; vol : volume

[1][intentionally skipped]
[2] The screening and baseline pre-dose assessments are performed over multiple visits but can be grouped or re-arranged as applicable
[3] Must be signed by the participant before disclosure. Study partner assent to be completed prior to completing cognitive assessments, and does not need to be on the same day as the study participant If informed consent is split into multiple signature pages, these may be signed over multiple days
[4] Participant must receive AD and study risk information before signing Informed consent
[5] Review remainder of study inclusion/exclusion criteria based on results of screening assessments since genetic disclosure.
/ Ensure eligibility is met up to baseline pre-dose assessments based on data not older than 12 weeks from randomization day[6] Circumstances where the Buccal Swab may not be performed are described in Section 6.1.2 and Section 6.1.6
[7] Including weight
[8] Complete at V101 if not available from previous 3 months. if administered by a non-certified rater record on paper form. If done by certified rater at V101 on Virgil tablet, then no need to repeat at V103
[9] At least four weeks from the previous cognitive assessment, RBANS Form A to be used at baseline and Form D at 3 months visit.
[10] To be completed within 2 to 7 days after both genetic disclosure and amyloid disclosure, by phone or on site if combined with the next visit. If disclosure is waived, [redacted]

[redacted] are waived. If 2-7 days follow up is waived or done by phone then corresponding eC-SSRS is to be completed continuing participants at next scheduled visit.

[11] See Section 6.1.2 and Section 6.1.6)

[12] Disclosure based on APOE4 carrier status - allow a reflection period post disclosure

[13] Amyloid status disclosure after results from amyloid status based on PET scan and/or lumbar puncture , allow a reflection period post disclosure

[14] To be performed in time to allow for results to be available prior to next visit.

[15] All ECGs to be taken in triplicate. During treatment period, ECGs to be taken approximately 2.5 hours after study drug administration at the site (see Section 6.4.5)

[16] Skin: In case of dermatological findings during skin examination: record corresponding dermatological AE and refer to photographs and scales for pruritus (Section 6.4.6)

[17] Numeric Rating Scales for pruritus only if pruritus present

[18] CDR and Diagnostic Verification/Classification to be performed by different raters for the same participant[19] Cognitive assessments should not be administered to the participant immediately after any potentially stressful procedures (e.g., blood draws, LP, imaging, amyloid disclosure session). Also, participants should not perform these assessments while fasting.

[20] Best effort should be exerted to perform assessments at the same time of the day for each participant as done for Screening / Baseline

[21] Study partner required to attend visit to complete relevant assessments: ECog is self-reported by the Informant, and CDR needs to be on-site for audio recording required for central review. [redacted]

[22] In case sedation is required for MRI or amyloid PET scans, allow for 72 hours before cognitive assessments. [redacted] For participants who consent to the Lumbar puncture, to be done after the corresponding MRI scan at month 24 and month 60.

[23] Site should allow sufficient time to receive MRI safety interpretation prior to performing the amyloid PET scan or lumbar puncture.

[24] Mandatory: lumbar puncture for CSF or Amyloid PET for eligibility

[25] Voluntary: Ensure participant consented to the additional optional procedures

[26] Expected for all eligible participants in the subset of sites that can access the tau PET tracer and have the required imaging capability

[27] Tau PET scan will be performed after amyloid status and disclosure is completed (HTs with elevated amyloid status and HM). Results of the tau PET is not required for eligibility. Refer to Section 6.5.3.2 to for conditions where tau PET is implemented In exceptional cases related to documented scheduling issues, scan can be performed within a maximum 4 weeks after the randomization date.

[28] Call IRT to register screening at ICF#B (as applicable), to notify screen failures/drug discontinuation as applicable.

[29] Randomization

[redacted]

[33] DVF at screening to be completed 5 days after the V103 CDR and RBANS to allow Central Review and feedback/queries closed before the PI completes the DVF (corrected scores for DMI and CDR global for the DVF). Diagnostic has to be verified as Unimpaired cognition BEFORE invasive procedures like MRI or later PET/LP.

[34] refer to Section 6.1.2 for specific Screening lab assessments

[35] The LP should be performed preferably in the morning and at 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 two hour after the LP for safety follow-up.

[36] [redacted]CSF, CSF cell counts, A beta40, A beta42, tau and P-tau, NFLs, others

[37] Conditional assessments to be repeated upon PPW/TEC: MRI and blood AD biomarkers if last ones were more than 6 months ago, and Lumbar Puncture if last ones were more than 18 months ago

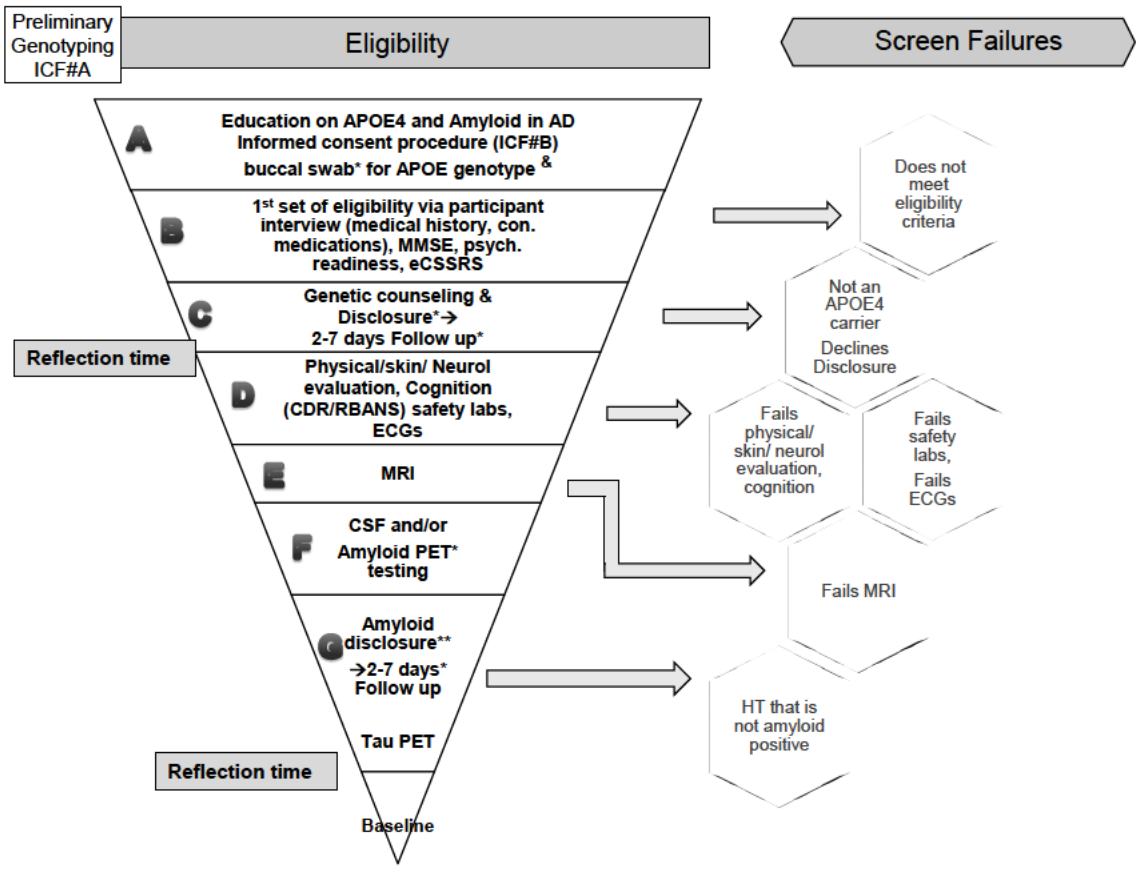
[38] Do not dispense at this visit as soon as target number of events is reached

[39] Y and Q represent Year and Quarters
[40] Assessments can be spread over several days
[41] Extended Treatment (to be scheduled until treatment completion for last participant)
[42] Treatment Epoch Completion (TEC) after early study termination all ongoing participants will come to their next scheduled visit to perform the mTEC visit. The tau PET and Amyloid PET scans are cancelled at the mTEC visit.
[43] within 12 weeks after mTEC visit. Can be converted to phone call in case of logistical constraints
[44] Interim compliance check over the phone or site visit, as needed. (Germany only: additional interim safety check at Week 6 including vital signs, physical/skin/neurological examination (to be recorded on source documents) and unscheduled eC-SSRS to be accessed on the vendor portal).
[45] Collect RBANS [redacted] until 4 weeks prior to month 6 if month 3 has already occurred at the time of implementation, [redacted]

6.1 Screening and disclosure process

In order to protect participants (e.g. from undue invasive procedures, to prevent disclosure of genotype for participants deemed not eligible for the study and to optimize operational efficiency at the site, screening assessments will be staggered and split into two screening parts. Screening part I: As part of the consenting process, individuals who present to the study site (with or without prior genetic information) will be informed (Figure 6-1 step A) about the study, the risk/benefits for investigational treatment, the mandatory genotyping for APOE (unless completed as preliminary under ICF#A or see Section 6.1.6) and the requirement to perform the amyloid status procedure(s). The participants will be informed that their individual APOE4 genotype and the corresponding risk estimates to develop AD will be communicated to them (under ICF#B). In addition, participants will be educated about the role of amyloid in AD and that the results of their amyloid status (elevated/non elevated) will also be communicated to them. A buccal swab will be performed if not done before (conditions described in Section 6.1.2, Section 6.1.6 and in Appendix 4).

Figure 6-1 Flow of screening steps



* Circumstances where the following assessment may not be performed are described in Section 6.1.6 and Section 6.1.2

** Homozygotes can elect to forgo disclosure of their amyloid results.

& if not done via ICF#A

Psychol.: Psychological, Labs: Laboratory evaluations, Con. Medications: concomitant medication

The study personnel will review the first set of eligibility criteria based on participant interview (Figure 6-1 step B). It is recommended that study personnel performing the 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.

Upon receipt of genetic results, counseling and disclosure (Figure 6-1 step C) for APOE genotype will be scheduled. 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. After the detailed counseling session, the genetic counselor (or such equivalent according to local regulations (e.g. study nurse or clinician)) will verify acceptance to receive disclosure before delivering the genotype results using the provided APOE risk information and talking points standardized across all sites. Genetic counseling is required even for those participants who already know their genotype, unless they learnt it from the pre-screening procedures for the API015A2201J study, i.e. received disclosure using the same standardized risk estimates.

Note: In case of screen failure before disclosure, genetic results will not be disclosed unless required per local regulations. In such case if the participant is psychologically ready and requests it, the disclosure will be organized per local clinical practice by the Investigator.

A follow up call will take place 2-7 days post disclosure for safety reasons to assess impact of disclosure. A few days' reflection period will be suggested to confirm willingness to continue with Screening part II.

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 (this applies also to subsequent amyloid disclosure), see Section 7.8.

Screening part II: Participants who have passed eligibility criteria related to safety and cognition (Figure 6-1, step D) will proceed to MRI (Figure 6-1 step E) followed by detection of brain amyloid status using lumbar puncture to collect CSF and/or Amyloid PET (Figure 6-1 step F). Restrictions related to these procedures need to be considered prior to scheduling these visits (see Section 6.1.2). After disclosure of amyloid results (information about elevated/non elevated brain amyloid, step G) a follow-up call /visit will be performed 2-7 days later. Another reflection period will be suggested prior to randomization. Although the APOE4 HMs will also undergo brain amyloid testing, they may elect to forgo the disclosure of their result since it is not required for their eligibility (Figure 6-1 see **).

6.1.1 Psychological readiness and follow up at screening ([redacted])

As part of the initial screening assessments, the psychological readiness of participant to receive their individual genotype results and corresponding risk estimates for AD, as well as their amyloid status during screening, will be assessed based on two scales: [redacted]

6.1.2 Source of genotyping, genotype result and genetic disclosure

While some participants have undergone APOE testing prior to screening (e.g. site database, biobanks, GeneMatch) all participants, must be genotyped using the Generation Program Central Lab buccal swab assay .The table below describes the requirements for genotyping, psychological readiness, genetic counseling and disclosure, 2-7 days follow up post disclosure, and availability of buccal swab results in relationship to randomization.

Table 6-2 Steps required around genetic testing and disclosure

Requirements	**From API015A2201 J (Generation Study 1)**	**Pre-existing registries, local databases Certified Lab results available[µ]**	**Pre-existing registries, local databases Certified Lab results available [µ]**	**- In study (De Novo) Genotyping - Genetic results documentation not available or not from a certified Lab**
Participant prior knowledge of their APOE Genotype	Known	Known	Unknown	Unknown
Must Meet Psychological Readiness Criteria (GDS/STAI-AD)	Yes	Yes	Yes	Yes
Perform Generation Study 2 Central Lab buccal swab	No*	Yes	Yes∞	Yes
APOE genetic counselling and disclosure	No (Allowed if participant desires)	Yes (Still completed regardless of prior knowledge)	Yes	Yes (Only after results from Central Lab are available)
2-7 days Follow up completed (GDS/STAI-AD)	No**	Yes	Yes	Yes
Results from Central Lab buccal swab must be available prior to Randomization	No	Yes	Yes∞	Yes

* if participant meets conditions in Section 6.1.6; if participant was disclosed in Generation Study 1 as a GeneMatch referral, then the Generation Study 2 buccal swab is required.

** Follow up already completed as part of Generation Study 1 Genetic Disclosure Follow-Up.

∞ can be waived if genotyping was performed with a Generation program Covance buccal swab kit

μ Lab result must contain information from the 2 alleles

6.1.3 Screening lab tests

In addition to the regular laboratory tests described in Section 6.4.4, the following test will be performed during screening:

- A buccal swab for APOE genotyping will be analyzed (under ICF#A as applicable) to determine APOE genotype and will also be stored for re-analysis with different assays / methods across all participants once the recruitment is completed to support the development of a potential companion diagnostics test if needed.
- A urine drug screen will be performed 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*), Hepatitis B and C (including reflex confirmation in case of positive IgG results), syphilis, and HIV may be performed if a previous result is not available from past 12 months as 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.

6.1.4 Assessment of brain amyloid status at screening

The last step of the qualifying assessments at screening will confirm brain amyloid status (elevated/not elevated). During the accumulation of amyloid into plaques in the brain of participants at risk for AD, the levels of several form Aβ species and tau / p-tau will change in the CSF collected by a lumbar puncture; and amyloid plaques will be detected by the amyloid PET radiotracers. The study allows either method for confirmation of brain amyloid status, which is required for enrollment of the HTs. For HMs the procedure is also mandatory even though elevated amyloid status is not required for eligibility. In exceptional circumstances, HMs can be enrolled in case of a contra-indication to lumbar puncture if no PET tracer is available. For APOE4 homozygote participants who opt out from amyloid disclosure, the 2 to 7 days follow up post amyloid disclosure is not applicable. The lumbar puncture CSF assay selected for the study will allow to run real time quantitative analysis of several forms of Aβ and tau / p-tau concentrations in the CSF. .. The lumbar puncture will be performed according to specific procedures described in the Laboratory Manual. The CSF samples collected will be sent to a central laboratory, where the selected validated assay will be used. The cut-off value to determine the amyloid status as elevated/not elevated will depend on the assay selected. The results will be provided to the clinical site. The remainder of the CSF collected will be frozen and stored as screening AD-related biomarker sample in all participants (even if they do not consent to further post-baseline CSF collection, or screen failed after the lumbar puncture was performed). The assessment of elevated brain amyloid from the central lab is required to document eligibility for APOE4 HTs.

An amyloid PET scan will be performed at the end of the screening period to confirm brain amyloid status, unless the participant already has documentation of elevated brain amyloid from a previous PET scan and the images are available for transfer and confirmation by the central reader at the imaging vendor.

Any of the established amyloid PET radiotracers used locally (e.g. ^{18}F-florbetapir, ^{18}F-Flutemetamol, ^{18}F-Florbetaben based on local regulations) can be used to assess brain amyloid status instead of (or in addition to) CSF levels of Aβ. The criteria for elevated brain amyloid will follow specifications for the specific radiotracer used. Once the PET images have been transferred to the imaging vendor, the scan will be assessed centrally by the Imaging vendor and results will be provided to the clinical site. The assessment of elevated brain amyloid from the central reader is required to document eligibility for APOE4 HTs.

[redacted] At least one screening amyloid measurement method is mandatory, additional testing for any method is voluntary at screening.

6.1.5 Assessment of unimpaired cognition at Screening: Diagnostic Verification Form

Criteria for diagnosis at screening will be assessed by the investigator (as described in Section 6.3.1) who will complete the diagnostic verification form (DVF) on the Virgil® tablet. The DVF must be completed as specified in Table 6-1. It is recommended to complete the DVF five days after CDR and RBANS have been completed at visit 103 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).

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

6.1.6 Other screening Considerations

In addition to the above, other assessments are to be performed during screening and/or baseline pre-dose as specified in Table 6-1, including efficacy and safety assessments described in Section 6.4 and Section 6.5 respectively.

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.

6.1.6.1 Screening extensions 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 Section 6.1.6 for potential re-screening in case of temporary conditions).
- Any screening (including Baseline) assessment supporting eligibility criteria must be performed within 12 weeks before the date of randomization. Assessments that are collected again during screening/baseline per Table 6-1, 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 or lumbar puncture to verify brain amyloid levels are valid without any limitation and do no 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 Baseline pre-dose, CDR is only collected once a V103 and needs to be repeated beyond 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 6.3.4 for APCC requirements during Screening.

6.1.6.2 Adapted screening flow for roll over participants from API015A2201J study

Table 6-3 describes assessments completed in API015A2201J study optimized for roll over participants. Concomitant Medications and Medical History have to be re-entered on eCRF and checked for any changes since API015A2201J interview. Similarly, V101 pre-disclosure scales & AD Baseline characteristics need to be re-entered in Virgil. Source data should document date of genotype disclosure in API015A2201J.

Table 6-3 Adapted assessment schedule for roll over participants from Screening 1 to Screening 3

Visit Name (visit numbers)	Scr1 (V101)	Scr2 (V102)	Scr3 (V103)
Informed Consent	ICF #B		
Medical History and ConMeds	Re-enter from API015A2201J interview, verify changes since last interview		
APOE buccal swab	Skip provided it was performed by the same central lab as for CNP520A2202J		
Previous Participant ID	Register API015A2201J participant number		
Vital Signs	To be measured		
AD BL charact	Re-enter from API015A2201J interview		
MMSE	Mark No if done <3 months or in GS1		To be administered
[redacted]	[redacted]		[redacted]
Genetic Disclosure		Skip	
ECG		To be measured	
[redacted]		[redacted]	
RBANS/Raven's			To be administered
CDR			To be administered
Ecog			To be administered
eCSSRS	To be administered		To be administered
Safety Laboratory evaluations		To be measured	
ECG		To be measured	

6.2 Screen failures, demographics/other baseline characteristics

6.2.1 Information to be collected on screening failures

Screening information including demographics, AD family history, genotype data collected, , unmet eligibility criteria, cognitive tests and serious adverse events (SAE) data collected need to be captured in eCRF for all participants, including those who have signed Informed Consent and have undergone genetic disclosure, but failed to meet eligibility criteria during screening and are not randomized.

AEs related to genetic disclosure will be captured in the eCRF, along with corresponding treatments or therapies. 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 and volumetric MRI obtained during screening will also need to be collected for participants who screen fail, as well as the amyloid PET assessment from central reader and/or CSF levels of Aβ used for eligibility assessment, when available.

6.2.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data are to be collected on all participants at screening, including: date (year only where applicable) of birth, sex, race, ethnicity, referral source, family history of AD, years of education and source of APOE genotyping including prior knowledge.

Relevant medical history/current medical conditions present before signing the Informed Consent will be recorded, preferably as diagnoses instead of symptoms, when possible. Investigators will have the discretion to record abnormal examination findings on the medical history eCRF when, according to their judgment, the examination abnormality occurred prior to the Informed Consent signature.

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

The AD-related history of the participant will be collected on the eSource (Virgil®) tablet. AD baseline characteristics captures family history of AD. Study partner information (relationship and frequency of contact with the participant) is part of the ECog-informant scale (see Section 6.3.8). Changes in study partner will also be collected on the eCRF.

6.2.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the participant. This information will be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.3 Efficacy

The frequency of assessments is described in Table 6-1.

All scales listed below and described later 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. The last assessment performed prior to randomization will be used as the baseline reference score.

- Diagnosis of MCI due to AD or dementia due to AD
- MMSE (also contributing to APCC)
- RBANS all domains (also contributing to APCC)
- Raven's Progressive Matrices – subset (also contributing to APCC)
- Clinical Dementia Rating Scale (Global score and Sum of boxes)
- [redacted]
- Everyday Cognition Scale (ECog)
- [redacted]
- [redacted]
- [redacted]

Cognitive testing must be administered by a clinician/rater certified by the rater training program of the dedicated Cognition vendor, including regular re-training. The selected raters will complete a pre-qualification survey. Criteria for granting "pre-qualification" status is based on their 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.

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

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 the cognitive and other test results (i.e. using a separate user ID on the Virgil® tablet) and should not be the Physician completing the DVF.

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 objectives (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, beside the audio recordings that will not be transferred to Novartis but destroyed after the end of the study.

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.

Paper versions are available in case of technical issue.

6.3.1 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 due to AD (Albert et al 2011) or dementia due to AD (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. However, with the six month visit intervals for cognitive assessments and potentially rapid progression in the participants at risk for clinical symptoms of AD, 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, 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), measures of daily function and measure of subjective/observer memory concerns (ECog – both informant [study partner] and participant versions), and other assessments (e.g. [redacted] MRI or other safety tests as needed). The investigator or deputy physician (sub-investigator) will complete the DCF on the Virgil® tablet with a narrative supporting his assessment.

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 detail in a specific charter.

The adjudication process will be triggered by:

- A change in diagnostic status as captured on the DCF on the Virgil® tablet; or
- Any increase from baseline on the global CDR score until a 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 cognitively unimpaired to MCI / 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 six-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). However, full cognitive assessments will only be conducted at the next scheduled visit to be scheduled at least four months from the previous cognitive assessment visit.

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 /dementia due to AD made at any time other than a six-monthly cognitive assessment visit will not trigger the adjudication process. The process will be triggered at the next cognitive assessment visit when the investigator updates the DVF or the results of cognitive assessments supporting the diagnosis as described above.

The adjudication process is briefly described below and further details can be found in the PAC charter (see Section 8.5). After the adjudication process has been triggered at a given visit, it will be repeated at the next scheduled cognitive assessment visit six months later to confirm the diagnostic classification. Once the diagnosis has been confirmed, the date of the initial visit that triggered the adjudication will be used to establish the event date for the TTE analysis. The event date and final diagnosis from the PAC will be captured in the database and used for analysis.

The PAC diagnoses will be communicated to the sites. If the PAC and the investigator do not agree on diagnosis, the PAC diagnosis will be used for analysis purposes.

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

6.3.2 API Preclinical Composite Cognitive (APCC) battery

The APCC score will be derived from the following seven tests performed as part of the cognitive scales administered during the study (see Table 6-1 Assessment schedule)

- 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 screening: first to assess inclusion (V101 and/or V103) 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 CDR and RBANS is required during screening to confirm unimpaired cognition (see Section 6.1.6.1), 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 2 for details on assessment from study partner and conditions of administration/presence at visits.

6.3.3 Mini Mental State Examination (MMSE)

The MMSE is a brief, practical clinician reported outcome that examines 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 zero 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 zero to five) will be used. MMSE will be performed at Screening part I first (by regular site personnel, no certification required) and then at baseline pre-dose and every 6 months by a certified rater. If MMSE is not available from previous 3 months source data, it should be collected a V101. If it is administered by a non-certified rater (allowed at V101 only) record on a paper form, do not upload to Virgil. If administered by a certified rater at V101 on Virgil, then no need to repeat at V103.

During the study, the test 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.

6.3.4 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 cognitively 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 (SD) 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 zero, confirming the absence of any clinically-detectable memory decline.

RBANS comes in four different versions labeled A, B, C, D. Form B will be used at screening (and repeat screening, if needed), while Form A will used at baseline, Form D at month 3 and Form C at month 6. Subsequent visits during the Treatment Phase will follow the pattern: Form D, B, A, C / D, B, A, C and so on.

6.3.5 Raven's Progressive Matrices

Raven's Progressive Matrices (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 zero to nine.

The Raven's will be administered using a paper-based stimulus booklet, results being captured on the Virgil® tablet.

6.3.6 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 zero to three, with greater scores indicating greater disease severity. CDR-SOB scores range from zero to 18 with greater scores indicating greater disease severity.

Clinician judgment of MCI due to AD or dementia due to AD and/or a change in the global CDR score (until the established diagnosis of dementia) will trigger the adjudication process (see Section 8.5).

[redacted]

6.3.8 Everyday Cognition Scale (ECog)

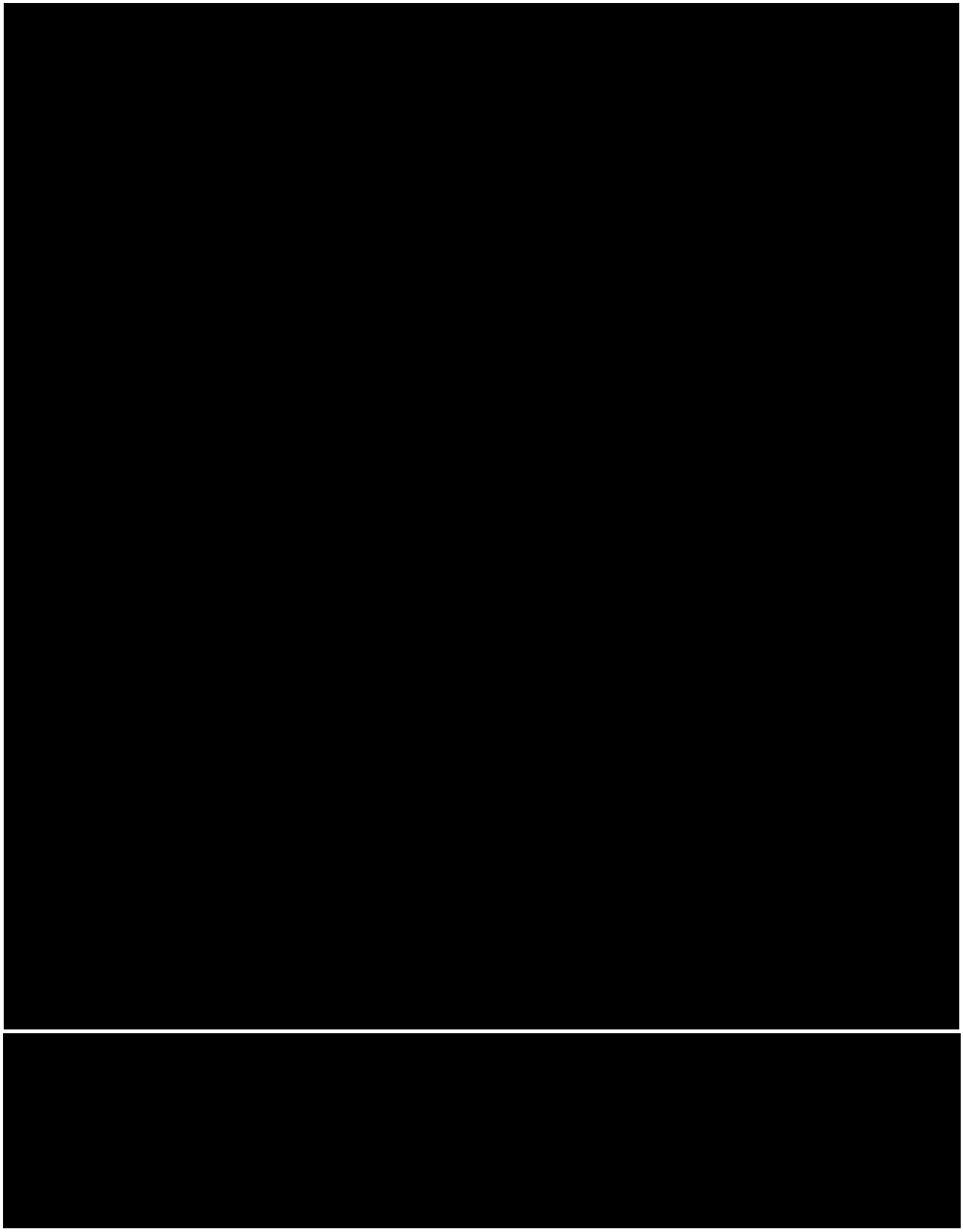
The ECog scale measures cognitively-relevant everyday abilities and is comprised of 39 items covering six cognitively-relevant domains: Everyday Memory, Everyday Language, Everyday Visuospatial Abilities, Everyday Planning, Everyday Organization, and Everyday Divided Attention (Farias et al 2008).

The questionnaire is a self-reported measure completed by both the participant (ECog-subject) and his/her study partner (ECog-informant). All questionnaires will be completed in the language most familiar to the respondent, at the scheduled study visit. The participant should be given sufficient instruction, space, time and privacy to complete the questionnaire on the tablet. The study coordinator (SC) should check the responses to the questionnaire for completeness and encourage the participant to complete any missing responses

Within each domain, ability to perform a specific task is rated on a five-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, six month intervals to minimize recall bias.

Details on the study partner characteristics (relationship and frequency of interaction) are also captured on the ECog-informant.



6.3.13 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 6.3.1, including a required confirmation at the consecutive 6-monthly visit and a formal adjudication process by an independent Progression Adjudication Committee (see Section 8.5).

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 due to AD and/or dementia due to AD. The APCC battery includes well-established, validated cognitive assessments that are expected to be sensitive to detect decline prior to the onset of MCI due to AD or dementia due to AD and continue to measure decline during the clinical course of the disease. The scales will undergo a central review to minimize variability across sites or raters throughout the study. 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 (Ropacki et al 2014). The derivation of the proposed APCC battery and its resulting test score is described in Section 6.4.2.

Secondary endpoints are chosen to evaluate the effects of the investigational drug on other clinical aspects of the disease with a focus on the endpoints likely to assess changes in individuals with preclinical AD and those who expected to progress to MCI.

CDR and its subscore CDR-SOB measure the global clinical function accounting for the input from the study partner which is widely used in clinical research in AD, RBANS total score is a clinical tool used to assess the neuropsychological status. 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.

Timing of the cognitive assessments at Screening and/or Baseline, 3, 6 and 12 months and then every 6 months will allow monitoring of cognitive, behavioral and functional status.

[redacted]

6.4 Safety

Clinically relevant findings that are present prior to signing Informed Consent must be included in the Medical History part of the CRF. Significant findings made after signature of the ICF which meet the definition of an AE must be recorded on the Adverse Event eCRF page for all participants randomized or treated.

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.

6.4.1 Physical (including skin) and neurological examination

Physical and neurological examinations will be performed by a qualified clinician at visits specified in Table 6-1. Any findings are to be recorded as unscheduled assessment/AE, as per Investigator judgement.

Physical examination will include an examination of general appearance, skin (and skin reactions), neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and vascular.

Neurological examinations will include mental status, cranial nerve 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 (see Section 6.4.6 for further information on dermatologic findings).

6.4.2 Vital signs

Vital signs include blood pressure, pulse, and temperature (using site equipment) 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 three minutes. The vital signs data will be recorded on the corresponding eCRF pages, unless marked for source documentation only in Table 6-1.

6.4.3 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.

6.4.4 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.

Please refer to Section 6.1.3 for additional laboratory tests required at Screening.

6.4.4.1 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 will be measured.

In addition if clinically warranted for participants treated with anti-coagulants, prothrombin time international normalized ratio (PT/INR) may be measured for assessment of coagulation at screening and repeated, if required.

6.4.4.2 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, creatinine, creatine phosphokinase (CPK), C-reactive protein (CRP), Vitamin B12, folate, gamma-glutamyl transferase (γ-GT), lactate dehydrogenase (LDH), cholesterol (total / LDL / HDL), triglycerides, lipase, α-amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glycated hemoglobin (HbA1c), blood urea nitrogen (BUN), uric acid, and thyroid stimulating hormone (TSH) 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 because of findings on previous MRI scans.

6.4.4.3 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 laboratory 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.

6.4.4.4 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.

6.4.5 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.

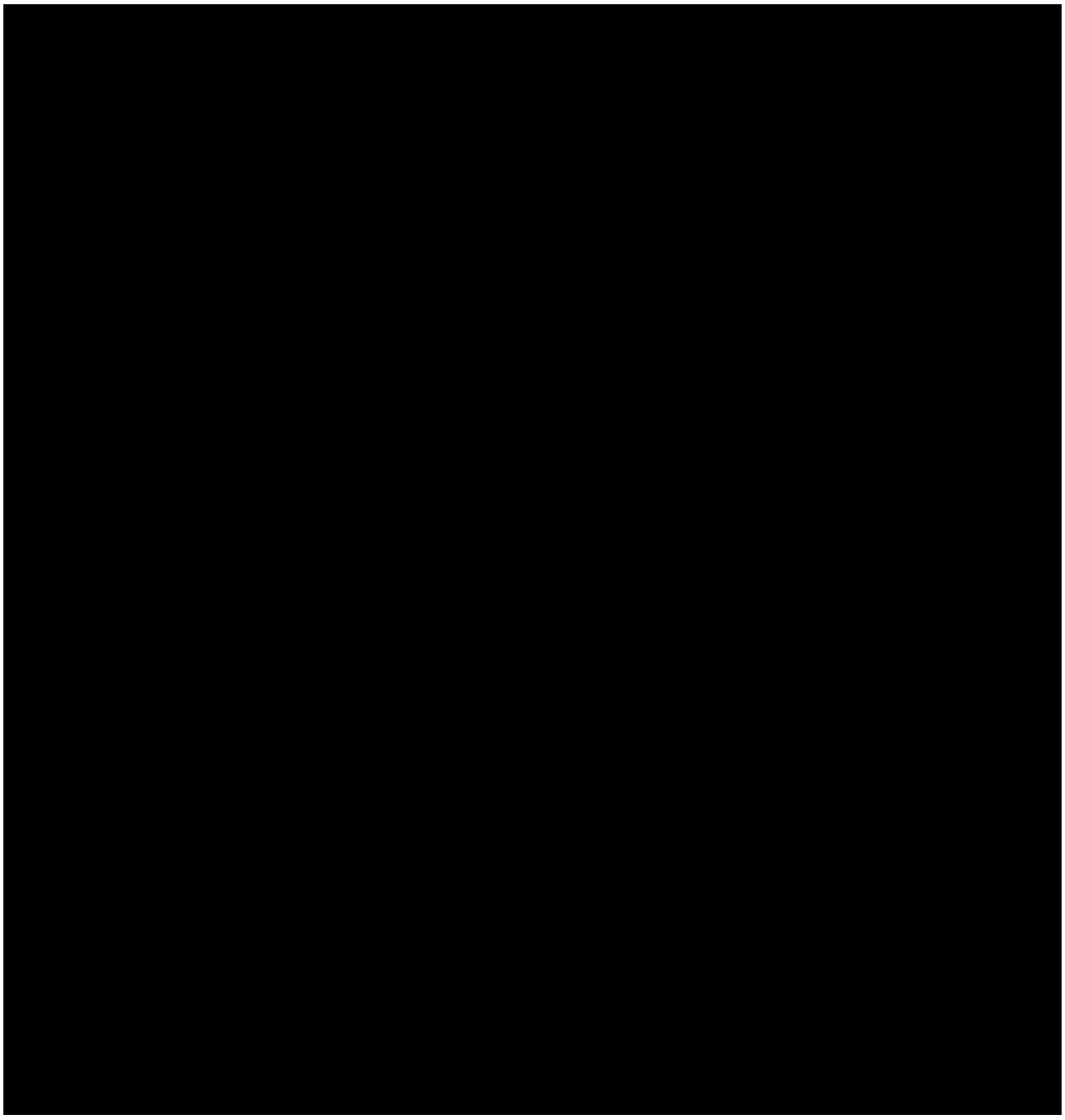
Twelve-lead standard ECGs will be recorded in triplicate (one minute apart) after participants have been resting in the supine position for at least 10 minutes. The ECGs should be scheduled approximately 2.5 hours post CNP520 drug administration on site (Section 5.5.4). If the LDR is 50 mg once weekly and the dosing day corresponds to the visit day then the scheduled is maintained otherwise, the ECG should be taken preferably at the same time of the day than earlier visits.

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Electrocardiograms will be obtained as designated in the Table 6-1, if applicable.

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

Each ECG tracing must be labeled with study number, participant initials, participant number, date and time, and filed in the study site source documents. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding and copies forwarded to the central ECG laboratory for assessment.



6.4.7 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 6.5.3.1. Note that this sequence will be captured twice at each scan, and may need a repeat in case of motion)
- Axial FLAIR (for general ascertainment of brain abnormalities including Amyloid Related Imaging Abnormality-Edema (ARIA-E) and for white matter lesions)
- Axial T2 Star/Gradient echo (GRE) (to assess Amyloid Related Imaging Abnormality-Hemorrhages (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). Diffusion Tensor Imaging (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 50 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 personnel) 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 in advance (i.e. at the latest 2 weeks prior) of the next drug administration/dispensing visit to verify safety findings before the bottles are dispensed.

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 Amyloid Related Imaging Abnormality (ARIA) (Sperling et al 2011) and white matter disease including hyperintensities (Wahlund et al 2001) will be provided to the site by the Imaging vendor as source documents at the investigator's site.

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®-Diethylenetriamine Pentaacetic Acid (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 Guidance to the investigators in case of newly occurring findings is provided in Appendix 1 Section 13.2.

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

6.4.8 Appropriateness of safety measurements

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.

In case of MRI findings indicating inflammation, additional clinical investigations including physical and neurological examinations and laboratory evaluations will be performed.

In relation to previously reported risks for other compound from the same class, regular skin examinations and centralized dermatological monitoring to assess skin reactions, are implemented.

Given the imbalance of pruritus observed in a previous study with CNP520, dermatological AE page and scales for itch and sleep disturbances are planned to capture those AEs in a systematic way. Management of pruritus is described in Section 6.4.6.2.

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

6.5 Other assessments

6.5.2 AD biomarkers

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. The results of the CSF biomarkers completed after baseline will not be disclosed to the participant nor to the investigator.

Blood-based biomarkers

Blood samples will be collected to explore blood biomarkers including gene expression associated with the treatment response to 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 $A\beta_{1-40}$ and NFLs in blood (plasma/serum) will be assessed at matching PK sampling time-point.

[redacted]

Timing of sampling of blood for AD biomarkers is listed in Table 6-1.

On dosing days, blood samples will be collected prior to study drug administration. 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.

CSF-based biomarkers

At screening, at least one amyloid measurement method (lumbar puncture or PET) is required for eligibility. Consenting for a second method of amyloid measurement at screening is voluntary. Participation in CSF collection for analysis of AD-related biomarkers is encouraged, but not mandatory. This is limited to participants who had a lumbar puncture at screening and will require a voluntary consent at each subsequent time point, year 2 and year 5.

For each participant, best efforts should be exerted to perform subsequent LPs 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 $A\beta_{1-40}$, $A\beta_{1-42}$, tau and p-tau_{181} and light chain neurofilaments (NFL) in CSF will be assessed.

[redacted]

6.5.3 Imaging biomarkers

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 be described in an imaging procedure manual that will be provided to the scanning centers with specific instructions for the acquisition of each imaging exam.

6.5.3.1 Volumetric MRI

The effect of CNP520 on brain volume (whole, regional and focal) will be assessed by means of T1 weighted, structural MRI scans performed as part of the safety brain MRIs described in Section 6.4.7 and performed on all participants. The change in volume of the hippocampus, lateral ventricles, and total brain will be measured specifically.

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 manual.

[redacted]

6.5.3.2 PET scans

PET scanning will be performed on a PET scanner meeting requirements specified in the PET Imaging manual. Procedural details will be provided to the participating PET imaging sites 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, but 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 specified for each radio-tracer will be specified in the PET procedure imaging manual.

The approximate scanning time, during which the participant will be lying on his or her back, will be 20 to 30 minutes, depending on the PET tracer. Participants will be supervised during each PET scan. CT scans will 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 biomarker data have the potential to unblind individual participants, the SUVR 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 scans

Cerebral amyloid burden and the effect of experimental treatment on cerebral amyloid will be assessed using specific amyloid PET radiotracers.

Amyloid PET scans will be performed at each timepoint year 2 and year 5 provided an amyloid PET scan with the same PET tracer was performed at screening. At screening at least one amyloid measurement method (lumbar puncture or PET) is required for eligibility. Consenting for a second method of amyloid measurement at screening is voluntary. The same radiotracer (either ^{18}F-florbetapir, ^{18}F-flutemetamol, or ^{18}F-florbetaben) will be used for all scans of given participant.

Date, time, batch, volume, and radiation dose of the radiotracer injection (according to the Imaging Manual) and any AEs occurring at the PET center will be recorded on the eCRF. For eligibility, a qualitative read will be performed by a central reader.

For biomarkers assessment, cerebral-to-reference region standard uptake value ratios (SUVRs) will be calculated for scans obtained at screening, month 24 and month 60, using pre-defined and automatically generated cerebral and reference regions-of-interest.

The quantitative SUVR results of the amyloid PET scans will not be disclosed to the site.

Tau PET scans

Tau PET, where available and locally permitted. (e.g. applicable for USA and Canada with 18F-flortaucipir only), will be performed to detect the effect of experimental treatment on neurofibrillary tangle burden. The same radiotracer (either ^{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.

Tau PET scans are expected at screening, month 24 and month 60 for participants from the subset of sites that can access the selected tau PET tracer and have the required imaging capability (i.e. tau PET scans are not required at sites without this access and/or capability).

Date, time, volume, batch, and dose of tau tracer, and any AEs occurring at the PET center and within the following 24 hours will be recorded.

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.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign including abnormal laboratory findings, symptom or disease) in a participant **after providing written informed consent** for participation in the study until EoS. Therefore, an AE may or may not be temporally or causally associated with the use of the investigational product. Similarly any untoward medical occurrence associated with genetic or amyloid disclosure in this study will be captured as an AE.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

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

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:
The severity grade 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 adverse events must 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) must be recorded.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study 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 (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the participant.

The investigator must also instruct each participant to report any new adverse event (beyond the protocol observation period) that the participant, or the participant's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

Laboratory test results

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

- They induce clinical signs or symptoms
- They are considered clinically significant
- They require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from screening or the previous visit, or values which are considered to be non-typical in participant with underlying disease. Investigators have the responsibility for managing the safety of individual participants and identifying adverse events. Alert ranges for laboratory will be listed in the central laboratory manual.

Refer to Section 7.8 for additional guidance on adverse events that may be related to genetic or amyloid disclosure, refer to Section 7.9 for additional guidance on major life events and to Section 6.4.6.2 for additional guidance on pruritus.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [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, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention.

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 it were more severe (please refer to 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 (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure participant safety, every SAE, regardless of causality to study treatment or to genetic or amyloid disclosure, occurring after the participant has provided informed consent and until 30 days after the last study visit/EOS or PPW must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit/EOS or PPW should only be reported to Novartis safety 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 occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded in English in the electronic Serious Adverse Event Report (eSAE) Form within the Oracle Clinical/Remote Data Capture (OC/RDC) system (whenever available and/or feasible) or on the paper SAE Report Form that should be used as back-up, especially in cases where there is no feasibility of the use of an eSAE Form. The investigator must assess the relationship of each SAE to 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 folder. Each re-occurrence, complication, or progression of the original event must 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 Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Drug Safety and Epidemiology 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 study 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 has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

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

Every liver laboratory trigger or liver event as defined in Section 13.3 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 13-3 and Table 13-4 in Appendix 1.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.
- These LFT repeats must 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 LFTs must 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 must be reported on the Liver CRF pages.
- If the elevation is confirmed, close observation of the participant 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 participant 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, consultancy of a hepatologist, based on investigator's discretion. All follow-up information, and the procedures performed must be kept as source and recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥24h) increase in serum creatinine of ≥25% compared to baseline during normal hydration status
- Urine event
  - new onset (≥1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥1+), hematuria or glycosuria

Please refer to Table 13-5 in Appendix 1 for complete definition of renal laboratory triggers and renal events. Every renal laboratory trigger or renal event as defined in Table 13-5 in Appendix 1 should be followed up by the investigator or designated personnel at the trial site.

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 (European Medicines Agency (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 7-1 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 Fertility control and pregnancy reporting

Participants eligible for this study will be 60 to 75 years of age, with women of childbearing potential being 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 as described in Table 6-1, including unscheduled visits.

A validated shorter version 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. Since this algorithm is dynamic, it cannot be administered on a paper form. 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 four or item five 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's ability to complete the eC-SSRS on their own, eg. in case of progression to dementia, the supplemental C-SSRS data eCRF page may be completed instead with input from the study partner.

In addition, all life-threatening events must 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 if the event was life-threatening. 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 must be reviewed by the DMC.

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 Novartis representative will review the protocol and eCRFs with the investigators and study site personnel. 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 records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study 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 Novartis Clinical Research Associate (CRA) organization.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs 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 data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/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 CRFs 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 study site personnel will enter the data required by the protocol into the Electronic Data Capture (EDC) system. Designated study site personnel 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 study site personnel. The investigator must certify that the data entered into the eCRFs 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 study team will review the data entered into the eCRFs by study site personnel 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 study site personnel are required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomic Therapeutic Chemical classification (ATC) classification system. Concomitant procedures, nondrug therapies and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Since the study includes specific genotyping requirement as APOE4 HTs and HMs at inclusion, the results of the genotyping performed at the central laboratory will be provided to the site and be part of the source documents for the participant. Results will also be sent electronically to Novartis.

Results for brain amyloid status from CSF Aβ and/or amyloid PET scans will be communicated to the site to confirm eligibility of HTs. The result (elevated/non elevated) will be captured in the eCRF.

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 scans for AD biomarkers will be analyzed centrally and the SUVR results will be sent electronically to Novartis. The [redacted] CSF samples analyses 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 the 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.

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 investigational drug 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 (DMC)

The program-level independent DMC will review unblinded safety, and tolerability data from all participants on an ongoing basis. Regular meetings will be scheduled on an approximately semi-annual basis aligned with the DMC meetings for the study API015A2201J, starting when safety data from first participant first post-baseline visit are available. Additional *ad hoc* meetings or off-line consultation may be scheduled as needed.

The DMC will be expected to provide recommendations on any of the following:

- Enhance safety monitoring
- Suspend treatment with current dose(s) of CNP520. In this case, the sponsor may switch participants to the LDR by activating the DRM.
- Stop the trial in case of (1) unexpected safety issues, (2) futility at pre-planned one of the two IAs, or (3) outstanding efficacy at one pre-planned IA on primary efficacy endpoints.

The safety parameters to be checked will be guided by potential and theoretical compound and class risks as described in the DMC charter, applicable until treatment termination.

The DMC may also assess any potential relationship (i.e. temporal) between exposure data for CNP520 with the occurrence of a particular AE of interest at the participant level if required, or identify signs or signals of safety concerns within the study and across studies with data from the API015A2201J study Cohort II with CNP520.

The DMC will also receive all SAEs and specific reports (including CDR, RBANS, MMSE and [redacted], centralized safety MRI scans, and volMRI), and any other reports as described in the DMC charter or requested ad hoc at any time by the DMC. The DMC may then access the treatment codes as provided in the DMC closed reports for each participant, to assess the relationship to study medication and assess criteria for suspension or design modification as described in the DMC Charter.

The DMC will be provided with individual participant's data, 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 external independent statistician.

8.5 Progression Adjudication Committee (PAC)

A process for the adjudication of MCI/dementia diagnoses will be implemented with an external PAC managed by the Cognition vendor. Details of the diagnostic criteria are described in Section 6.3.1 and a description of the PAC members, role, and function will be described in the PAC charter applicable until treatment termination. The same PAC membership and operating rules that apply for the API015A2201J study will also apply for this study as well.

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 in the PAC charter.

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

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

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 and/or amyloid disclosures)) and making recommendations regarding changes or adjustments
- Providing summary reports to the DMC prior to each data review meeting summarizing any findings related to the safety monitoring of genetic and/or amyloid disclosures.

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

9 Data analysis

The final analysis will occur once the overall targeted number of events for the study has been reached and all participants have completed their month 60 assessments.

In general, data will be reported by treatment arms of interest and by visit as applicable. Summaries including only baseline data, may also include a total group (All participants). In case of no DRM, treatment arms of interest are the originally defined treatment arms #1 to #3. In case of DRM, summaries will show the following treatment arms of interest: the pooled active treatment arms (Arm #1 and Arm #2) and placebo (Arm #3). In addition, summaries may also include the sub-group of participants randomized to any of the two active treatment arm after the DRM, i.e. those who started on the LDR.

In general, descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables . The number and percentage of participants in each category will be presented for categorical variables.

The primary treatment arms for efficacy analysis will include the following participants based upon whether or not the DRM will be implemented.

- In the case that the DRM does not occur, the 3 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 1:1. 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 #1, 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, namely 2:1:2 for Arm #1: Arm #2: Arm #3. The primary placebo arm (Arm #3) consists of all the participants who have been randomized to Arm #3 and received placebo regardless of DRM. The primary active arm (pooled Arm #1 and Arm #2) consists of the following participants
    1. those who received CNP520 50 mg once daily dose followed by CNP520 LDR (those who were originally randomized to Arm #1, and subsequently switch to the lower dose regimen) and
    2. those who received CNP520 15 mg once daily dose followed by CNP520 LDR (those who were originally randomized to Arm #2, and subsequently switch to the lower dose regimen) and
    3. those who received CNP520 LDR dose only (those who were randomized to active treatment arm after the 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 Full analysis set (FAS) will consist of all randomized participants who started 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.

All efficacy analyses will be conducted on data from all participants in the FAS. All safety analyses will be conducted on data from all participants in the SAF.

9.2 Participant demographics and other baseline characteristics

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

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

9.3 Treatments

In case of no DRM, for both doses of CNP520 and placebo, data for investigational drug administration will be summarized and listed. In case of DRM, summaries will contrast the treatment groups of interest and 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 ATC classification) and by treatment arm of interest, and be listed.

9.4 Analysis of the primary variables

In case of no DRM, the primary active arm is the 50 mg active arm and the secondary active arm is the 15 mg active arm. In case of DRM, the primary active arm will be defined by pooling of the two active treatment arms (Arm #1 and Arm #2), a secondary treatment arm will not be defined. The primary analysis will contrast the primary active arm vs. placebo. This primary comparison will be embedded into a closed testing procedure that will be applied to both scenarios, with and without DRM.

There are two primary endpoint variables: time to first diagnosis of MCI due to AD or dementia due to AD and the APCC test score. Success of the trial will be determined by a positive result **in at least one** primary endpoint on the primary treatment arm dose to be used for the primary analysis vs. placebo.

To control the overall family-wise type I error rate (FWER) an appropriate multiplicity adjustment procedure using a closed testing strategy will be applied to the analyses of the primary efficacy variables. The procedure will take into account testing two endpoints, two active arms vs. placebo and the IA on primary endpoints. This strategy to preserve the overall FWER at $\alpha = 5\%$ (two-sided) is described in Section 9.7.

9.4.1 Primary Variable(s)

Two primary variables will be used:

- TTE, defined as the time to first confirmed diagnosis of MCI due to AD or dementia due to AD. TTE will be calculated as the time from randomization to the first confirmed diagnosis. For each event (confirmed diagnosis), the date of the initial investigator diagnosis will be used to establish the date of the event (neither the date of adjudication (see Section 6.3.1), nor 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 where the diagnostic classification has been assessed. Time to censoring date will be calculated from day 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 zero 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 analysis to address the primary objective comprises statistical tests of hypotheses of both primary endpoints. The statistical tests will compare the primary active arm of the investigational treatment vs. placebo at the appropriate α-level. These primary analyses are embedded as part of the overall testing procedure described in Section 9.7.

For the primary active arm (1) of the investigational drug, the following two null hypotheses will be tested corresponding to the two primary endpoints:

- $H_{01(1)}$: The primary active arm does not differ from placebo with regard to the distribution of time to first diagnosis of MCI due to AD or dementia due to AD;
- $H_{02(1)}$: The primary active arm does not differ from placebo in the mean change from baseline to month 60 in the APCC test score;

The corresponding alternative hypotheses are:

- $H_{A1(1)}$: The primary active arm differs from placebo with regard to the distribution of time to first diagnosis of MCI due to AD or dementia due to AD.
- $H_{A2(1)}$: The primary active arm differs from placebo in the mean change from baseline to month 60 in the APCC test score.

In a similar way, $H_{01(2)}$ and $H_{02(2)}$ and corresponding alternative hypotheses are also defined for the secondary active arm (2) in case of no DRM.

Time-to-event

After the target overall number of events has been reached and after all participants have completed their month 60 visit or PPW, the team will agree on the exact cut-off date/point for the final analysis. The final TTE analysis will include data until this cut-off point. Any data collected after this cut-off point will not be used for the primary analysis of TTE. That means specifically that only confirmed events collected up to the data cut-off point will be counted. Confirmation information collected after the cut-off point to confirm an earlier (meaning before the cut-off point) adjudicated diagnosis of MCI or AD due to dementia will not be taken into consideration. As a consequence, the observation will be censored at the last date prior to cut-off point that the TTE endpoint was evaluated, and the unconfirmed diagnosis will not be counted as an event in the primary analysis.

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.

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

Terms will be included for the following effects:

- treatment arm
- baseline value of the APCC test score
- age group (60 to 64 years, 65 to 75 years) at Baseline
- region (North America, Europe, Asia, Other)
- genotype (HM, HT)

APCC

The final primary analysis of the APCC score will use data from the FAS.

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 baseline covariates as fixed effects:

- treatment arm
- time as the discrete variable scheduled (mapped) visit window
- baseline APCC test score
- age group (60 to 64 years, 65 to 75 years) at Baseline
- region (North America, Europe, Asia, Other)

- genotype (HM, HT)

and the following interaction terms:

- treatment arm × visit window
- baseline APCC test score × visit window

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

Visit windows used as a factor in the MMRM will correspond to all scheduled visits for which participant level data for the parameter was expected. Thus, all available data including data from visits after Month 60 will be used in the model.

NOTE: While the method used to identify amyloid positive HTs is included as a level in the genotype stratification variable, it is not included in the abovementioned genotype factor in the primary analysis models for the two primary endpoints. The potential effect of the method is investigated separately as supportive analyses, specified in Section 9.4.4.

9.4.3 Handling of missing values/censoring/discontinuations

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

Primary analysis

In general, an observation will be censored if no confirmed event has been observed prior to the TTE analysis cut-off point. 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 PH model) for the TTE endpoint assumes censoring at random for participants not having an event.

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 that prematurely discontinued the treatment epoch due to an AE, death, or unsatisfactory therapeutic effect (UTE).

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, 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 (60 to 64 years, 65 to 75 years) at Baseline
- region (North America, Europe, Asia, Other)
- genotype (HM, HT).

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.

9.4.3.2 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.

Primary analysis

The primary analysis method (MMRM) for APCC will assume missing data to be MAR.

Sensitivity analyses

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.

Sensitivity analyses will be conducted for the following scenarios in which 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 such missing data 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 abovementioned reasons for missingness;
- 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.
- A further sensitivity analysis under a plausible missing not at random (MNAR) process will also be conducted. 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 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, 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.

9.4.4 Supportive analyses

Censoring data after discontinuation of study drug

A TTE comparison of the primary active arm of CNP520 vs. placebo will be performed on the FAS, taking into account whether a participant had continued, interrupted or permanently discontinued study-drug during the study. For this analysis, 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.

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

1. For participants having completed the study: the last day of his/her final diagnosis assessment visit, that is at the final visit during the follow-up epoch when a diagnosis assessment occurred,
2. For participants ongoing in the study 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).
3. For participants who permanently discontinued from study drug, but still being followed up: The last day of a diagnosis assessment up to 12 weeks after the last day of study drug administration. Any data beyond the abovementioned 12 weeks will be excluded from this TTE analysis.

For study drug interruptions lasting longer than 12 weeks, assessments of diagnostic classification during this period, but beyond the abovementioned 12 weeks will be excluded from the derivation of the TTE endpoint. Assessments subsequent to resuming drug administration (on-treatment) will be included in the derivation.

The first subsequent on-treatment assessment will then be used to define a change in diagnostic classification and the TTE as follows:

1. If the result antecedent to the first excluded result was adjudicated as a change in diagnostic classification, then the subsequent on-treatment assessment result will serve as the confirmation assessment if it was also assessed as a diagnosis and the date of the antecedent assessment will serve as the event date.
2. If the result antecedent to the first excluded result was not adjudicated as a change in diagnostic classification, then if the subsequent on-treatment assessment was adjudicated as a change in diagnostic classification and also confirmed subsequently, then it will serve as a confirmed adjudicated event, but the date of the event will be defined as the date of the first excluded result.

Other analyses on the time-to-event endpoint

A non-stratified log-rank test will be conducted to compare estimates of the hazard functions of the treatment arms.

In order to understand the potential longitudinal difference in the rate of disease progression by genotype, a longitudinal Cox PH model will be implemented as an important primary supportive analysis. This will be done by including the additional interaction term treatment arm × genotype × visit window.

Excluding data after discontinuation of study drug in APCC

As with the primary analysis method (MMRM) for APCC, this analysis will assume missing data to be MAR.

Within this analysis, the following data will be excluded (regarded as missing though it is available) and thus implicitly assumed to be MAR:

- Data retrieved from participants remaining in the treatment epoch beyond 12 weeks after permanent study drug discontinuation
- For intermediate study drug interruptions lasting longer than 12 weeks, off-drug APCC data during this period, but beyond the abovementioned 12 weeks. Assessments subsequent to resuming drug administration will be included in the analysis.

In addition to this analysis, the same tipping point, controlled imputation and ‘copy reference’ sensitivity analyses as planned for the primary analysis will be conducted, but additionally excluding the off-treatment data to be missing as mentioned above.

Other analyses on 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 includes the same factors, but also including the additional interactions (and underlying factors)

- baseline hippocampal volume | visit window
- genotype (HM, HT) | visit window | treatment

The primary analysis will be supported by an MMRM similar to the primary model, but using 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 in terms of transient interaction with cognitive readouts.

Treatment interaction with CNP520 will be assessed as follows:

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

Other supportive analyses

In order to understand the possible difference in outcome due to the method of classifying amyloid status of HTs at baseline, a Cox PH model and MMRM model for APCC will be conducted. The models will include treatment arm as a factor, while adjusting for genotype and classification method (PET or CSF).

Sub-group analyses

Analyses similar to the primary 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 2018 Early Alzheimer's disease: Developing Drugs for Treatment

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.

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 (amyloid and tau), Volumetric MRI, tau and p-tau in CSF. All of the secondary endpoints will be analyzed using longitudinal models such as a mixed measures repeated model (MMRM) for the CDR-SOB similar to the approach for the primary endpoint APCC with treatment as factor and adjusting for important covariates.

9.5.1 Efficacy variables

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

A multiplicity adjustment will also be applied to the key secondary variable, as specified in Section 9.7.

The following null hypothesis will be tested for the selected dose within the framework of the multiple testing strategy:

- $H_{03(1)}$: 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:

- $H_{A3(1)}$: 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. It is planned to apply an MMRM adjusted for important factors similar to the approach for the primary analysis model as specified for the APCC. Further specifications will be given in the statistical analysis plan (SAP).

The adjusted least square means (LSMs) for each treatment arm, the difference between the LSMs (active vs placebo), the 2-sided p-values (unadjusted for multiplicity) and associated confidence intervals (CIs) 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.

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 in ECog total score will be presented over time. An analysis of change from baseline will be also performed using longitudinal MMRM model as described for APCC scores 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. An analysis of change from baseline will be also performed using a longitudinal MMRM model as described for APCC score in Section 9.4.2.

[redacted]

9.5.2 Safety variables

All 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.

AEs, SAEs and Death

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, and 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 arm. These descriptive summaries will be presented by laboratory test category, visit, and treatment arm.

Shift tables will also be provided in which 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 arm.

Vital signs

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

Electrocardiogram (ECG)

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

Safety brain MRI scans

Descriptive summaries 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 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.

9.6 Interim analyses (IAs)

The main purposes of the planned IAs are safety monitoring, dose adaptation and assessment of either futility or overwhelming efficacy with the potential consequence of discontinuing one active treatment arm or the whole study. Safety data from CNP520 in the API015A2201J study as well as learnings from external data which are 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	Semi-annual (and additional ad hoc reviews as needed)	All safety data as determined by the DMC.
CNS activity futility analysis	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 and CSF and blood biomarkers
Primary efficacy futility analysis	Once approximately 75% of the target 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 as follows:

1. Safety review:
   a. Regular semi-annual evaluation of safety parameters and worsening in cognition as a safety measure throughout the study duration
   b. During the recruitment period, safety and tolerability will also be assessed for a potential DRM.
2. Review of CNS activity for futility based on the following biomarkers:
   a. Volumetric MRI: hippocampal volume
   b. CSF: Aβ, tau and p-tau
   c. PET : tau tangles
   d. NFLs in blood / CSF
3. Review of primary endpoints (TTE and APCC test score) to assess futility or overwhelming efficacy

9.6.1 Interim analysis for biomarkers of CNS activity

CNS activity of CNP520 will be assessed by means of one unblinded interim analysis performed by the DMC for futility based on treatment difference from baseline in CSF (Aβ, tau, p-tau) and volumetric MRI (e.g. hippocampal volume) at 24 months. The unblinded IA will consist of a pooled analysis across studies API015A2201J (Cohort II) and CNP520A2202J, and also separated by genotype. Additional AD related biomarkers obtained at 24 months post-baseline may be used to support decision making.

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 24 months post baseline. This preliminary sample size is based on exploration of the change over 24 months from the longitudinal data from Alzheimer's disease Neuroimaging Initiative (ADNI) cohort data.

The exact futility decision rules will be based on further investigation of internal and external data. Specific decision criteria, sample sizes and the exact timing of the analysis are under investigation and will be outlined in the DMC charter and pre-specified in the DMC master analysis plan (MAP) prior to the corresponding IA.

The main purpose of this IA is futility. No alpha spending strategy will be employed.

9.6.2 Interim analysis for primary endpoints

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 of the primary endpoints.

The main purpose of this IA is futility. Nevertheless, since this involves unblinding of data on the primary endpoints, a small portion of 1/1000 of the overall significance level alpha of 5% will be spent to control the type-I error rate using a Bonferroni split (that means 0.004% and 0.001% for TTE and for APCC, respectively). The underlying idea is to set the hurdle very high such that an early stopping due to efficacy can only occur when an extremely large treatment effect is observed. Efficacy of APCC will be considered as overwhelming only if it is supported by at least a convergent trend on TTE and additional data generated outside of this trial supporting the clinical meaningfulness of the APCC. Decision on futility will also be based on meeting the futility rule for the TTE endpoint. The decision should be strengthened by consistent results for the TTE endpoint in a pooled futility analysis including also data from the API015A2201J trial as well as for the APCC. Stopping for futility based on APCC only is not foreseen.

The IA will be based on available data on the two primary parameters: time to first diagnosis of MCI/dementia due to AD and the APCC. The IA is planned to be conducted 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 at 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 the number of events (total across all treatment arms).

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 IA on primary endpoints. 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 IA on primary endpoints will be pre-specified and be outlined in the DMC charter and the DMC MAP prior to the IA.

9.7 Multiplicity and adaptation adjustment

Main strategy

To ensure control of FWER of $\alpha = 5\%$ (two-sided), the multiple testing procedure will account for the following:

1. Testing hypotheses on two primary endpoints - $H_{01(i)}$ and $H_{02(i)}$, where *i* represents the two doses
2. Testing two doses of CNP520 versus placebo - $H_{0j(1)}$ and $H_{0j(2)}$, where *j* represents the two primary variables

The familywise error rate (FWER) due to testing the four hypotheses on two primary endpoints and two active doses will be controlled by the closed testing procedure (Marcus, et al 1976).

For an intersection of two hypotheses, which test an active dose against placebo on the same endpoint, data of the two doses will be pooled across the two dose levels. This pool will be treated as a single “treatment group” to be tested against placebo.

The multiplicity arising from testing two different endpoints (APCC and time-to-diagnosis) will be handled by a Bonferroni adjustment: At a global level, APCC will be tested at a level of 1% and time-to-diagnosis at a level of 4%.

Combining these approaches of a Bonferroni adjustment and separate closed-testing procedures guarantees that the FWER is controlled at $\alpha = 5\%$ (two-sided).

The fact that the protocol allows a DRM will not be accounted for in the statistical testing procedure. Strictly speaking, the option of the DRM is a pre-planned potential adaptation to the design, limited to the dose regimen and the definition of primary treatment arm, but keeping other design features and the statistical analysis strategy stable. The potential adaptation has been pre-specified based on current knowledge, not driven by data of the ongoing clinical program. Specifically, the selection of the dose regimen options (before and after DRM), has not been informed by blinded or unblinded data of the program. The total sample size, the number of treatment arms, the randomization ratio across arms, and the testing strategy will remain unchanged regardless of the DRM. Hence, it is assumed that bias due to DRM will be minimal and can be ignored in the statistical analysis (see also Section 3.3).

The proposed closed testing procedure starts with testing the global intersection hypothesis. If this hypothesis can be rejected, testing of hypotheses of the next levels is possible while keeping the overall type-1 error rate. The elementary hypothesis (lowest level in the hierarchy of hypotheses) can be tested if all hypotheses of higher levels containing this hypothesis have been rejected at the corresponding error rate. In case of DRM, the testing stops after rejection of the primary hypothesis of interest, the elementary hypothesis to compare the original active treatment arms vs. placebo are not of interest (see Appendix 5).

Key secondary endpoint inclusion into the testing procedure

If the global null hypothesis for the primary endpoints is rejected (i.e. if either the pooled TTE test is significant at 4% or the pooled APCC test is significant at 1% in the default scenario), then the key-secondary endpoint CDR-SOB will be tested at alpha=5% using the same closed testing strategy outlined in Appendix 5.

False rejection of the global null hypothesis for the primary efficacy (successfully rejecting the at least one of hypotheses for the primary endpoints) as well as for the global key secondary hypothesis is thus controlled at alpha=5%.

Additional details

Multiple safety interim analyses are foreseen to mitigate the risk to participants over the treatment duration in case the benefit/risk expectations of CNP520 are not likely to be met.

An adjustment of the FWER α (5% two-sided) will be performed only for the IA based on primary endpoints, which allows for early stopping due to exceptional efficacy. A small portion of 1/1000 of the FWER of 5% will be spent for the IA on primary endpoints with the intent to pre-define a high hurdle for early stopping. Hence, the actual alpha level to be used in the final closed testing procedure analysis will be slightly smaller than 5% (thus 4.995%), but for simplicity's sake this has been ignored in the above description of the testing procedure (see Section 17 Appendix 5).

Since regular DMC related analyses target primarily the safety of the participants without the intent to stop the study due to efficacy or any other modifications of the subsequent study conduct related to efficacy, no alpha adjustment is required.

Similarly, the biomarker based futility analysis is only assessing CNS activity, but not the primary endpoints. Therefore, this IA for CNS activity cannot lead to early stopping of the trial due to exceptional efficacy and an adjustment of the FWER is not required.

9.8 Sample size calculation

A total of 2000 participants will be randomized into the study, with a sample size of 800 for the initial target dose of CNP520 50 mg once daily and placebo, respectively, thereby achieving a 1:1 ratio for this initial primary dose regimen of CNP520 50 mg once daily vs. placebo. Sample size calculations were mainly based on reaching a target power of 80% for the test of the elementary hypothesis on the TTE endpoint for the 50 mg once daily dose of CNP520 vs. placebo.

Type I error rate alpha and power

The FWER α will be 5% (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 on the two primary endpoints 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 (0.004% and 0.001%, respectively) of the error rates will be spent in a 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.

Sample size calculations were mainly driven by power considerations for the primary endpoint time to first diagnosis of MCI or dementia due to AD, based on the planned recruitment time of two years and variable observation period of five to seven years. The power, i.e. the probability to detect a true difference between treatment arms, was set to be at least 80% for this analysis.

The power for the primary analysis does not account for the potential and non-negligible inflation of the type II error due to futility analyses using biomarkers and the primary efficacy endpoints. On the other hand, the potential inflation of the type II error due to the option for DRM is expected to be minimal and hence, has been ignored for the calculations of sample size.

Simulations

The sample size 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 estimates 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, Memory and Aging Project, or the Minority Aging Research Study);
- Longitudinal data from the National Alzheimer's Coordinating Center (NACC), Washington University which specifically included a sub-group of APOE4 HMs- or HTs in the age range of 60 to 75 years.

- Longitudinal data from ADNI which specifically included a sub-group of APOE4 HMs or HTs amyloid positive carriers participants who are cognitively normal at baseline and in the age range of 60 to 75 years.
- Longitudinal data from AIBL which specifically included a sub-group of APOE4 HMs or HTs with elevated brain who are cognitively normal at baseline and in the age range of 60-75 years.

Brain amyloid status is determined by using measurements of Aβ in the CSF or brain amyloid PET scans. Since amyloid status information is available only from ADNI and AIBL cohort data, accordingly, the lower bound estimates for the expected event rates were taken from cohorts without amyloid status (Rush, NACC) and the upper bound estimates were taken from cohorts with amyloid status (ADNI, AIBL).

The cohort data were the basis 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 trials have been simulated to investigate the power under different assumptions, as for instance on the age distribution. An age distribution of 1:4:3 for the age groups 60 to 64, 65 to 69, and 70 to 75 has been chosen which holds the quota of a maximum of 20% of participants in the lower age group. The observed event rate in five years in the simulated trials was about 30% which is in line with the assumption on the event rate in five years in the target population of 25 to 35%.

Sample size calculation based on the primary endpoint time to MCI / dementia due to AD

The sample size calculation for the TTE 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:

- two years accrual period,
- five to seven years observation period,
- 30% of participants experiencing an event in the control group in 60 months observation period,
- a hazard ratio of 0.75 in favor of the active treatment arm,
- 30% drop-out rate over 60 months (corresponding to a yearly drop-out rate of about 6.9%),
- $\alpha = 4\%$, two-sided test.

Power has been investigated for the comparison of the CNP520 50 mg once daily dose versus placebo using a log-rank test under Lakatos approximation. Based on the above-mentioned assumptions, a sample size of 1600 participants (800 participants in the 50 mg once daily CNP520 dose group and placebo, respectively) need to be randomized to achieve at least 80% power. The targeted number of events required to be observed in the active treatment arm is 180 and that placebo group is 228 adding up to a total of 408 target events for the comparison of the primary active arm versus placebo in case of no DRM. Assuming the same underlying event rate of 22.5% in the two active treatment arms, the targeted number of events in the secondary active arm is calculated as 22.5% of the total number of participants in the arm (i.e. 90 events). Supposing a total of 2000 participants randomized, the overall targeted number of events is 498 (= 228 + 180 + 90). This target total number of events also defines the target number of events for primary analysis in case of DRM. Due to blinding across all three treatment arms, the statistical analysis will only be performed after the total target number of events has been observed. This applies to both situations, with and without DRM. The power estimation using the log-rank test provides a conservative estimate and should thus be interpreted as the lower limit of power.

In the simulation setting, the trial data were simulated using models which included certain prognostic factors. This enabled the investigation of different population assumptions and allowed each subject to have its own TTE distribution depending on baseline characteristics. The power estimates based on the adjusted Cox PH model hence were overly optimistic and should be interpreted as the upper limit of power which may only be reached in a best case scenario. Power for the TTE endpoints reached 89% and more in simulations depending on the underlying assumptions on the population.

The above calculation was done using the commercial software PASS 2008.

Power calculations based on the primary endpoint APCC

Power considerations for the APCC have been based on the MMRM model generated from the simulated trials and on standard power calculation based on a t-test. The following assumptions for the power calculations based on the change from baseline to month 60 in APCC were used:

- Statistical test used: t-test (standard) and MMRM (simulations),
- 30% drop-out rate over five years,
- Target power of 80%,
- $\alpha = 1\%$, two-sided test.

The sample size of n = 800 participants in the selected CNP520 dose arm and placebo, respectively, is sufficient to detect an effect size of 0.20 with 80% power. Results from simulations indicate that using a longitudinal model and adjusting for prognostic factors will increase power to detect an effect size of 0.20.

Power calculations for APCC using the two-sided t-test have been performed with nQuery Advisor 7.0.

Power in case of DRM and overall power

In case of DRM, the primary analysis will compare pooled active treatment arms vs. placebo. Treatment effect will be assumed to be similar across different treatment regimen of CNP520 as described in Section 3.3. Hence, the target number of events is the same as for the situation without DRM. Due to the higher number of participants included in the primary analyses, power will be higher in case of DRM compared to without DRM.

The overall power to detect a true treatment effect in at least one of the two endpoints is higher as compared to the power for the single endpoints. The difference in power between the dual and single endpoints is largest when the endpoints are independent and will be small when the endpoints are strongly positively correlated.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations (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 (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. The participant must 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 (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators, in a separate document, a proposed informed consent form that complies 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 the Novartis monitor after IRB/IEC approval.

A preliminary consent for collection of the buccal swab for genotyping of APOE is provided for sites who need to select from the general population and need to establish their local database. The study includes optional assessments for biomarkers (amyloid PET scans and/or CSF post-baseline) that will be captured in the main informed consent, requiring separate agreements if the participant agrees to them. 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 assent by signing the main informed consent as such. 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.

[redacted]

Special requirement for assessing the participant's capability to consent

Where required by the Health Authority (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 (i.e. lumbar puncture and/or PET scans at months 24 and 60). This process will involve a qualified person who will deliver the questionnaire "Assessment of capacity to consent to the participation in the study CCNP520A2202J" 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 months 24 or 60, should not undergo these specific procedures even if they had consented to them originally. Their study participation should nevertheless be continued if authorized by local regulations. Administration of investigational treatment, other less invasive procedures like blood sampling or MRI, and attending the protocol-specified visits can continue as planned.

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 5.6.2 in case of progression to late-moderate or severe dementia.

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 must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (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 Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, 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 immediately that this request has been made.

10.4 Publication of study protocol and results

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.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

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 is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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.

11.1 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 participant 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 must be followed.

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13 Appendix 1: Clinically notable criteria

13.1 Clinically notable test values and vital signs

13.1.1 Vital signs

Table 13-1 Clinically notable vital signs

Variable			Change relative to baseline
Heart Rate	> 120 bpm	and an	increase of ≥ 15 bpm
	< 50 bpm	and a	decrease of ≥ 15 bpm
Systolic BP	> 180 mm Hg	and an	increase of ≥ 20 mm Hg
	< 90 mm Hg	and a	decrease of ≥ 20 mm Hg
Diastolic BP	> 105 mm Hg	and an	increase of ≥ 15 mm Hg
	< 50 mm Hg	and a	decrease of ≥ 15 mm Hg
Weight			change of ≥ +/- 7%

13.1.2 Clinically notable ECG and laboratory values

Abnormal ECG values will be specified in the manual from the centralized ECG vendor, with specific telephone alert values and panic alert values.

Figure 13-1 Abnormal ECG measurements leading to exclusion alerts

Category	Values leading to exclusion alerts
HR_MN	< 40 or > 120
Mean QRS interval	> 140 ms
Mean QTcF interval	> 500 ms

Abnormal laboratory values will be specified in the manual from the central laboratory with specific telephone alert values and panic alert values.

The Novartis Medical Monitor will be notified by email and fax at the same time as the investigator for all types of alerts.

Discontinuation of study medication, for individual participant, is required in case of clinically significant ECG or laboratory findings considered to be suspected to be related to study medication, as judged by Investigator or the DMC, respectively.

Table 13-2 Abnormal laboratory values leading to participant exclusion

Organ	Laboratory value	Limits
Liver	ALT or AST	> 5 × ULN
	ALP	> 2 × ULN (in the absence of known bone pathology)
	TBL	> 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST and INR	> 3 × ULN and > 1.5

Organ	Laboratory value	Limits
Renal	Estimated glomerular filtration rate (GFR)	<30mL/min (calculated using the Cockcroft-Gault formula)
Blood (chemistry)	Calcium (mg/dL)	<7.0; >12.5
	Phosphorus (mg/dL)	<2.0
	Sodium (mmol/L)	<125; >155
	Potassium (mmol/L)	<3.0; >6.0
	Magnesium (mg/dL)	>3.0
Blood (Hematology)	HGB (g/dL)	<8.0; ≥19.0
	WBC (GI/L)	<2.0; ≥13.0
	Platelets (GI/L)	<50; ≥700

13.2 Neurological symptoms or signs

New neurological findings are defined as clinical signs or symptoms that raise concern in respect to neurological conditions.

They include but are not limited to:

- significant new or worsening neurological symptoms or signs, as reported spontaneously by the participants/caregivers at any time, or detected during the scheduled physical/neurological examinations or on MRI scans. These might be events such as new or worsening peripheral neuropathies, visual disturbances, or seizures;
- worsening of cognition not consistent with the previous clinical course, as reported spontaneously by the participants/caregivers at any time or observed at the clinical assessments (e.g. APCC, CDR-SOB, RBANS, NPI-Q).

Investigators will be asked to review the finding in consultation with an appointed neurologist (when applicable) and initiate any additional tests as needed. Summary of the findings will be provided for the attention of the Safety Monitor who will assess the need to consult the DMC, regardless of the suspected relationship to investigational treatment.

Further tests will be scheduled to monitor the time-course of the findings until resolution if possible, and detailed information on the results will be communicated to the DMC.

Discontinuation of study medication will be considered in case of clinically significant findings considered to be suspected to be related to study medication, as judged by investigator and DMC.

These findings will be reported additionally as AEs only if they are symptomatic (i.e. reported spontaneously and not only observed at scheduled assessments), require symptomatic treatment, or impact study medication (suspension or discontinuation).

In case MRI findings indicating CNS inflammation, additional clinical investigations including physical and neurological examinations and laboratory evaluations will be performed. Final interpretation of the safety MRI scans, including assessment of ARIA, white matter, stroke or other findings will be provided to the site by the Imaging vendor.

13.3 Liver and renal event and laboratory trigger definitions and follow-up requirements

Note: Tests below are recommended to be performed at a local lab for a faster result availability. However, if required exception testing by central lab can also be organized even if they are not part of the regular laboratory testing.

Table 13-3 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT / AST ≤ 5 x ULN 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN ALP > 2 × ULN (in the absence of known bone pathology) TBL > 2 × ULN (in the absence of known Gilbert syndrome) ALT or AST > 3 × ULN and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) Any clinical event of jaundice (or equivalent term) ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 13-4 Follow-up requirements for liver events and laboratory triggers

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 5 to ≤ 8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for more than 2 weeks, discontinue the study drug Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (participant is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the participant	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (participant is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the participant	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study treatment immediately Hospitalize the participant Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Consider study treatment interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Table 13-5 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider participant hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor participant regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

14 Appendix 2: Role of study partner and key site personnel

Study partner

The study partner is expected to spend sufficient time with the participant to be familiar with his/her overall function and behavior, and be able to provide adequate information about the participant including: (a) knowledge of domestic activities, hobbies, routines, social skills and basic activities of daily life; (b) work and educational history; (c) cognitive performance, including memory abilities, language abilities, temporal and spatial orientation, judgment, and problem solving; (d) emotional and psychological state; and (e) general health status.

Although the study partner is expected to accompany the participant to all relevant visits, if unavailable to attend a given site visit (e.g. if traveling or sick), his/her input to clinical scales can be organized via a telephone interview [redacted]. Yet for CDR and ECog, a site visit is preferable

The study partner and/or the participant will be requested to call the site to inform about any study partner unavailability or transition to a new one. Of note: a study partner needs to be identified and documented before the next study treatment dispensing visit, otherwise the study treatment would be suspended until a new partner is identified.

The study partner is excluded from participating in any study in the Generation Program (CCAPI015A2201J and CCNP520A2202J). The study partner may only be a participant if another study partner can be identified. A participant cannot act as study partner for another participant.

Key study personnel

Key site personnel include (but are not limited to) the following individuals:

Investigator

The investigator will be responsible for:

- Overall conduct of the study at the study site including assigning per protocol required study site personnel
- Organization of the referral and recruitment strategies at the site level (see also Appendix 4)
- Organizing for the genetic disclosure as per local regulations if not done by genetic counselor (see below genetic counselor description)
- Organizing for the disclosure of the Amyloid status test results to the participants after receiving the results on elevated or non-elevated status from the centralized assessment performed by the central reader at the Imaging vendor.
  Of note: the local read should never be communicated to the participant.
- Management of the routine clinical care of the study participants
- Confirmation of participant's eligibility for randomization
- Supervision of study drug dispensing. The investigator may delegate this responsibility to the Study Nurse/Study Coordinator as appropriate and permissible by local regulation

- Oversight of the raters performing the clinical assessments, review and interpretation of the results to support diagnosis of MCI or dementia. Timely completion of diagnosis verification form on the Virgil tablet.
- Management of adverse events and treatment decisions
- Ensuring that all site personnel are informed of concomitant medications excluded per protocol (see Section 5.5.8)
- [redacted]

Occasionally, the investigator may designate other medical personnel/health care professionals (other than the Independent CDR rater, e.g., a back-up physician or Study Nurse/Study Coordinator) at the study site to perform some of the tests and evaluations listed above. The investigator is also responsible for ensuring access to appropriate expertise for consultation (e.g. dermatological findings, ECG interpretation, mental health care) during the study as needed.

Study Nurse/Study Coordinator (SC)

The Study Nurse/Study Coordinator's responsibilities may include:

- Assisting the investigator in participant management, including the assessment and treatment of adverse events, symptom progression and the recording of adverse events, concomitant medications and monitoring of compliance (counting of remaining capsules left over in bottles returned by the participant, uploading data from the electronic cap)
- Scheduling visits and assessments as outlined in the protocol, maintaining proper source documentation and transcription of the data to the CRFs
- Coordination with and between the study selected central labs, drawing, processing and shipping lab and biomarker samples
- Providing participant with an Information Card (identifying study participant in a clinical trial with pertinent information and site contact information)
- Entering data in the eCRF
- Retrieving required source information from the other units or departments (Radiology, Nuclear Medicine, lumbar puncture, Genetic counseling...)
- Performing ECG and uploading results to the central cardiology vendor
- Placing calls to IRT upon screening, randomization and drug dispensing visits, or PPW/EoT
- Administering the Virgil tablets: registering raters and participants and visits on the Cognition vendor portal.
- Coordinating the completion of the eC-SSRS on the ERT website

Genetic counselor

- Providing the genetic counseling about risk estimates for AD based on genotype for APOE, along with epidemiology and latest information available, using the standardized talking points and AD risk estimate materials provided at the study level.

- The genetic counselor as well as the rater who assesses the psychological readiness with GDS and STAI-AD before disclosure are expected to be blind to the actual APOE4 genotype for the participant until disclosure occurs.
- Once readiness of the participant to receive their individual information is confirmed, the counselor will obtain the genotype result and disclose it to the participant.
- Confirming to the SC that disclosure occurred and/or follow-up steps required.

Raters

Raters will be certified by the cognition vendor based on their qualifications and previous experience in rating the APCC scales. Training may be required in addition at study start, and regular re-training will also occur during the course of the study.

The initial MMSE at first Screening visit to verify a score >24 for inclusion can be performed by a non-certified rater (eg. Study Nurse or Study Coordinator) and be performed on paper not transcribed to the Virgil tablet in such case. Other scales which are not contributing to the APCC can also be administered by a non-certified rater or by the CDR rater.

Requirement for separate raters:

At least three different raters are needed for any given cognitive assessment: a CDR rater, a rater for other APCC scales, a physician to complete the diagnostic evaluation. The certified raters at the site will administer the clinical scales using the tablet provided by the Cognition vendor.

A separate rater for CDR scale is required, so that CDR rating is blinded to the other APCC scales' results.

The physician who completes the diagnostic evaluation form should not have administered the CDR at that given visit.

MRI technician

The MRI technician will be responsible for:

- Familiarization with the MRI manual procedures and the study specific MRI protocol
- Proceeding with the calibration and qualification steps required by Imaging vendor
- Performance of high-quality MRI scans using the study specific parameters stored in the designated MRI scanner for the duration of the study
- Submission of the MRIs in the appropriate format to the Imaging vendor for assessment by the central MRI reader

Nuclear Medicine Specialists

The NM technician will be responsible for:

- Familiarization with the PET manual procedures and the study specific PET protocol for amyloid radiotracer(s) available for the site
- Proceeding with the calibration and qualification steps required by Imaging vendor

- Performance of high-quality PET scans using the study specific parameters stored in the designated PET scanner for the duration of the study
- Submission of the PET scans in the appropriate format to the Imaging vendor for centralized assessment.
  Of note: local evaluation SHOULD never be communicated to the participant.

Lumbar Puncture specialist

Lumbar punctures should be performed by a qualified and experienced specialist (e.g. anesthesiologist or physician) with regular practice of lumbar punctures.

The procedure and details on possible side-effects and minimization methods will be described to the participant upfront.

16 Appendix 4: Recruitment methods

It is anticipated that there will be different methods of recruitment, with site and/or country specificity. Some potential participants will already be part of a local/regional/national registry. Some potential participants will be known to investigators as the relatives of affected participants. Some may be self-referred from an initial assessment/memory check (e.g. subjective complains or concern due to familial history) or because they are already aware of their APOE4 genotype (e.g. from private genetic testing companies).

Additionally, country specific programs may potentially be offered. For example, in the US, potential participants may be referred to a trial-independent APOE genotyping program. This program will apply an algorithm to invite APOE4 carriers (HMs and HTs) and non-carriers that meet basic eligibility criteria to participate in this study.

Table 16-1 Referral source of participants

Referral method	Participants referred for screening part I and genetic disclosure
1) Potential participants with previous genotype information and genetic disclosure performed in the API015A2201J study	HTs will still have to undergo amyloid testing and disclosure in screening part II. See Section 6.1.2
2) Pre-existing registries/local databases with available and previously disclosed genotype information, as per local clinical practice; informed consent allows for re-contact for potential clinical trial participation based on the genotype.	HTs and HMs will be invited to the screening part I including the genetic counseling and disclosure despite their genotype knowledge to ensure the same process and counseling steps are followed. The buccal swab will need to be repeated at the study central laboratory even with appropriate confirmed documentation of genotype. See more information in Section 6.1.2
3) Pre-existing registries/local databases with available but not disclosed genotype information; informed consent allows for re-contact.	HTs, HMs and a sufficient proportion of non-carriers will be invited to attend the screening visit part I. The exact ratio of each genotype will not be disclosed to the participants in order to prevent implicit disclosure by invitation. During the initial contact with participants inviting them to the screening part I, it must be highlighted that those with and without the genotype of interest are invited at this stage. See more information in Section 6.1.2
4) *De novo* genotyping: Newly identified potential participants, without prior genotype information.	The investigator will assess the most efficient way* to identify HMs and HTs to build a local database according to the local regulations and in collaboration with the Sponsor. A buccal swab will be performed to obtain the APOE genotype under the preliminary informed consent ICF#A. The genotyping will be performed at the central laboratory. The site will identify a dedicated recipient of the genotype results as described above for scenario 3. Not all participants that perform the genetic testing will be disclosed*.

*The process will be documented in the local study file. Such a process will be site/country-specific. The person delivering the genetic counseling and disclosure should be qualified according to local regulations

APOE4 = Apolipoprotein E4; HM = homozygote; HT= heterozygote.

17 Appendix 5: A testing strategy with option for dose regimen modification and two endpoints

17.1 Design and definitions

At randomization, participants are randomized to two active doses, CNP520 50 mg once daily (*H*) and CNP520 15 mg once daily (*L*) and a placebo control (*C*) in a 2:1:2 ratio into the 3 respective treatment arms. In case of no DRM, the CNP520 50 mg once daily dose arm is considered as the primary active arm, that is, the active arm to be used for comparison with placebo in the final primary analyses. In case of DRM, the primary active arm will be defined by pooling of the two active treatment arms (pooled P: H and L). The primary efficacy analysis furthermore consists of two endpoints (*e)*, Time-To-Event (TTE) and API Preclinical Composite Cognitive Battery (APCC), designated as $e = T, A$.

A DRM may be triggered upon DMC recommendation and/or Sponsor's decision. The DRM will be a modification to lower either dose strength or dosing frequency. This lower dose regimen is referred to as the LDR.

In case that no DRM occurs, the 3 treatment arms remain the same as planned originally. The primary treatment arms are CNP520 50 mg once daily or matching placebo in a respective ratio of 1:1.

In case the DRM is implemented, the same randomization ratio is maintained. The primary active arm (pooled across all active arms) consists of the following participants:

- those who received CNP520 50 mg once daily dose followed by CNP520 LDR (those who were originally randomized to Arm #1, and subsequently switch to the lower dose regimen) and
- those who received CNP520 15 mg once daily dose followed by CNP520 LDR (those who were originally randomized to Arm #2, and subsequently switch to the lower dose regimen) and
- those who received CNP520 LDR dose only (those who were randomized to active treatment arm after the DRM).

The trial then proceeds to the final analysis and only at the final analysis, a statistical test of the treatments L, H or P vs C is performed. The preplanned testing strategy follows the closed test principle (Marcus et al 1976).

Definitions and abbreviations:

- Comparisons of treatment vs. control: $i = L, H, P$, where *L* denotes the comparison of the low dose vs. placebo control *C*, *H* the comparison of the high dose vs. placebo control and *P* the comparison of the pooled high and low dose vs. placebo control.
- Endpoints: $e = T, A$ where T is the time to diagnosis and *A* the composite endpoint APCC.

- A single null hypothesis of no effect of treatment comparison i on endpoint e is denoted by H_e^i.

  Intersection hypotheses are denoted by concatenating the index pairs $\frac{i}{e}$ of each hypothesis,

for example, $H_{TTA}^{LHH} = H_T^L \cap H_T^H \cap H_A^H$.
An intersection hypothesis that reference both treatment arms for an endpoint e are abbreviated as $H_e^P = H_e^L \cap H_e^H$. Whenever such a pair occurs it will be collapsed to one hypothesis since the data will be pooled and a single test conducted, for example, $H_{T,T,A}^{L,H,H} = H_{T,A}^{P,H}$.
Thus, the 15 intersection hypotheses resulting from the 4 original elementary hypotheses on 2 doses and 2 endpoints can be rewritten with either one or two index pairs.

- P-values resulting from the 4 univariate tests across both stages are denoted as p_e^i for, $e = T, A; i = L, H$, while p-values for the 2 possible pooled tests on the 2 endpoints are denoted as $p_e^P, e = T, A$.
  P-values resulting from tests on first and second stage data are accordingly denoted by $p_{e,j}^i, e = T, A; i = L, H; j = 1,2$ and $p_{e,j}^P, e = T, A; j = 1,2$.
- Pooling of doses refers to pooling of all participant data initially randomized to both the 50 mg and 15 mg once daily dose arms, irrespective of dose regimen changes during the course of the trial.

17.2 The closed multiple testing procedure

To test the four elementary hypotheses H_e^i with familywise error rate control, a Bonferroni based closed test procedure will be used on the $2^4 - 1 = 15$ intersection hypotheses. This section describes the closed testing procedure. The Bonferroni test is only needed to control the type I error for the multiplicity incurred by the two endpoints (with unknown correlation). The multiplicity due to the two doses in an intersection of two hypotheses on the same endpoint is taken care of by pooling the data from the two dose levels.

The following general rules apply:

- Any intersection hypothesis involving both endpoints, T and A is rejected if either the test for T is significant at level $\alpha_T = 4/5\alpha$ or if the test for A is significant at level $\alpha_A = 1/5\alpha$.
- An intersection hypothesis involving only one endpoint can be tested at full level α.
- An elementary hypothesis can be rejected if and only if all intersection hypotheses containing it can be rejected at full level α.

Table 17-1 Closed test for the standard design option

Hypothesis index no.	Hypothesis	Reject if
1	$H_{TTAA}^{LHLH} = H_{TA}^{PP}$	$p_T^P < \alpha_T \vee p_A^P < \alpha_A$
2	$H_{TTA}^{LHL} = H_{TA}^{PL}$	$p_T^P < \alpha_T \vee p_A^L < \alpha_A$
3	$H_{TTA}^{LHH} = H_{TA}^{PH}$	$p_T^P < \alpha_T \vee p_A^H < \alpha_A$
4	$H_{TAA}^{LLH} = H_{TA}^{LP}$	$p_T^L < \alpha_T \vee p_A^P < \alpha_A$
5	$H_{TAA}^{HLH} = H_{TA}^{HP}$	$p_T^H < \alpha_T \vee p_A^P < \alpha_A$
6	$H_{TT}^{LH} = H_T^P$	$p_T^P < \alpha$
7	$H_{AA}^{LH} = H_A^P$	$p_A^P < \alpha$

Hypothesis index no.	Hypothesis	Reject if
8	H_{TA}^{LL}	$p_T^L < \alpha_T \vee p_A^L < \alpha_A$
9	H_{TA}^{LH}	$p_T^L < \alpha_T \vee p_A^H < \alpha_A$
10	H_{TA}^{HL}	$p_T^H < \alpha_T \vee p_A^L < \alpha_A$
11	H_{TA}^{HH}	$p_T^H < \alpha_T \vee p_A^H < \alpha_A$
12-13	$H_e^L, e = T, A$	$p_e^L < \alpha$
14-15	$H_e^H, e = T, A$	$p_e^H < \alpha$

The above test procedure has the following property: If a hypothesis related to one of the endpoints can be rejected for both the high and the low dose arm, the hypotheses related to the other endpoint can be tested at full level alpha. This is illustrated with an example:

Assume that H_T^H is rejected at α_T, then it implies that each of the intersection hypotheses with H_T^H are also rejected at α_T (that is, hypothesis indexes 1, 2, 3, 5, 6, 10, 11 . This is the case if $p_T^P < \alpha_T$ and $p_T^H < \alpha_T$. In order to reject H_A^H, the intersection hypotheses 1, 3, 4, 5, 7, 9, 11, must be rejected.

If hypothesis 9, H_{TA}^{LH}, is not rejected because $p_T^L > \alpha_T$ then in order to reject this intersection hypothesis we must have $p_A^H < \alpha_A$ to declare H_A^H rejected at FWER α. If, however both hypothesis related to the T endpoints can be rejected for both the high and the low dose arm, then in order to reject, for example, H_A^H, it is sufficient that the tests of the intersection hypotheses 7, H_A^P, and of the hypothesis H_A^H are significant at level α.

In case of no DRM, the primary analysis comprises testing of hypotheses H_T^H and H_A^H. In case of DRM, the testing strategy stops earlier: the primary analysis comprises testing of hypotheses reject H_T^P and H_A^P.