2 Synopsis

Name of product: CNP520

Study number: CCNP520A2202J

Title of study: 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)

Principal Investigator: 5.1.2.e [redacted]

Study center(s): 195 centers across 24 countries.

Publication (reference): None

Study period

Study initiation date: 03-Aug-2017 (first participant first visit)

Early termination date: 11-Jul-2019

Study completion date: 26-Mar-2020 (last participant last visit)

Phase of development (phase of this clinical study): II/III

Objectives: Worsening in some measures of cognition was the trigger for early termination of the study and objectives are therefore described before the primary endpoints:

- To assess the effect of CNP520 vs. placebo on cognition and reversibility using Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score, API Preclinical Composite Cognitive Battery (APCC) score and Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB).

Primary objectives

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

Key secondary objectives

- 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 RBANS.
- To demonstrate the effects of CNP520 vs. placebo on function.
- To demonstrate the effects of CNP520 vs. placebo on Magnetic Resonance Imaging (MRI) measures suggestive of cerebral amyloid angiopathy (CAA).*
- To demonstrate the effects of CNP520 vs. placebo on brain atrophy.
- To demonstrate the effects of CNP520 vs. placebo on AD-related biomarkers.

**This secondary objective was not reported*

Methodology: The study was a randomized, double-blind, placebo-controlled, parallel group, adaptive design with variable treatment duration planned in cognitively unimpaired participants aged 60 to 75 years, with at least one APOE4 allele (homozygotes (HMs) or heterozygotes (HTs)) and, if HTs, with evidence of elevated brain amyloid. The participants were randomized to either CNP520 50 mg (Arm 1) or CNP520 15 mg (Arm 2) or placebo (Arm 3) in 2:1:2 ratio.

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 were staggered, organized across 7 visits that could be re-arranged and split into two screening parts:

1. Screening part I: This included the less invasive assessments i.e. participants were assessed for APOE genotype. Participants who confirmed as psychologically ready received disclosure of their risk estimate to develop clinical symptoms of AD based on their age and genotype. A single disclosure follow-up was scheduled 2-7 days after the genetic disclosure (GD). Only APOE4 carriers continued to Screening part II.
2. Screening part II: This included safety assessments, various cognitive and neuropsychological scales, brain MRI scan, blood biomarkers, amyloid PET scan and/or lumbar puncture (either one was mandatory at screening to determine brain amyloid levels), and disclosure of amyloid status (optional in HMs), with follow-up 2-7 days later. The optional assessments included tau positron emission tomography (PET), cerebrospinal fluid (CSF)-based biomarkers, blood-based biomarkers (serum plasma, blood for pharmacogenomics (ribonucleic acid (RNA) and pharmacogenetics (deoxyribonucleic acid (DNA)).

Treatment epoch

The randomization was stratified based on age, region, genotype, and method used to determine amyloid status.

Number of participants (planned and analyzed): 2000 participants were planned to be enrolled in the study. Overall 8970 participants entered screening, of whom 1172 participants completed the screening phase. A total of 1145 participants entered the treatment epoch by the time study was terminated: 689 on CNP520 total (456 on CNP520 50 mg and 233 on CNP520 15 mg) and 456 on placebo. Results are presented for CNP520 total pooled group across the 2 doses in this report.

Diagnosis and main criteria for inclusion:

Participants eligible for inclusion were male or female, aged 60 to 75 years inclusive, at the time of signing the informed consent. The inclusion criteria included: being APOE4 carriers (both HMs and HTs), with the additional requirement for HTs to have elevated brain amyloid levels as ascertained by amyloid PET imaging or lumbar puncture; being cognitively unimpaired; assessed as psychologically ready and willing to receive their individual results for APOE genotyping and amyloid status; having a study partner.

Duration of treatment: In this study, participants were planned to be treated for at least 60 months (5 years) up to a maximum of 96 months (8 years), and no longer than the time until the target number of events for the time-to-event (TTE) endpoint had been observed and confirmed in the respective cohort. However, due to the early termination of the study this planned treatment duration was not achieved.

Test and reference therapies, dose and mode of administration, batch number:

CNP520 hard gelatin capsules for oral administration (p.o.) were supplied to the Investigators at dose strengths of 15 mg and 50 mg. Matching placebo was supplied as hard gelatin capsules of similar size and appearance as CNP520. All test materials were supplied by Novartis. The batch numbers of the test drug/investigational product, active comparator and placebo are presented below:

Study drug and dose strength	Batch number
CNP520 15 mg	5.1.1.c
CNP520 50 mg	5.1.1.c
Placebo	5.1.1.c

Criteria for evaluation

Efficacy: gehele paragraaf 5.1.1.c

Pharmacokinetics:

5.1.1.c

Safety: gehele paragraaf 5.1.1.c

Biomarkers: gehele paragraaf 5.1.1.c

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Statistical methods:

Due to the early termination of the clinical trial, most of the primary, key secondary and secondary objectives could not be analyzed with the data collected up to termination. Since no data at Month 60 have been collected, the originally planned inferential statistical analyses comparing efficacy readouts at Month 60 across treatment groups were not conducted, but data collected on primary and secondary variables were reported descriptively, as available. Worsening in cognition and assessment of reversibility after drug wash-out was reported as a part of the efficacy analysis.

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There were two primary endpoint variables:

- TTE, with event defined as time to first confirmed diagnosis of MCI due to AD or dementia due to AD (whichever occurs first), and
- Change in the APCC, from baseline to Week $260_{(M\ 60)}$

The key secondary endpoint variable was CDR-SOB.

Other endpoints included the following variables:

- RBANS total score and index scores
- MMSE
- Raven's Progressive Matrices
- ECog-Subject and ECog-Informant
- NPI-Q
- Biomarkers in CSF
- Biomarkers in blood: serum light chain neurofilaments (NfL) and $A\beta_{40}$
- PET Standard Uptake Value Ratio (SUVR) and centiloids

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Summary - Results

Demographic and background characteristics:

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Efficacy and biomarker results:

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Pharmacokinetic results: 5.1.1.c

Safety results:

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Conclusion:

The study was terminated early due to unexpected, mild, early worsening in measures of cognitive function, increased brain volume loss, and greater mean body weight loss on CNP520 compared to placebo.

CNP520 treatment was stopped due to an early signal of potential harm to study participants, which could be studied through the off-treatment follow-up period to demonstrate reversibility of the findings.

The early study termination prevented achieving its pre-planned objectives, so potential efficacy of CNP520 to prevent progression to clinical symptoms of AD could not be assessed. The long-term effects of CNP520 remain unknown.

History of changes to the synopsis			
Version	Date (content final)	Summary of Changes	Change to overall conclusion
1.0	19-Feb-2021	Original version	