A Phase 2a, Proof-of-Concept, Open-Label Study to Evaluate the Pharmacodynamics, Pharmacokinetics, and Safety of Obicetrapib in Patients with Early Alzheimer*s Disease (Hetero/Homozygote APOE4 Carriers)

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Ethical review	Approved WMO
Status	Completed
Health condition type	Mental impairment disorders
Study type	Interventional

Summary

ID

NL-OMON51159

Source
ToetsingOnline

Brief title
Obicetrapib in early Alzheimer's disease (Hetero/Homozygote APOE4 Carriers)

Condition

- Mental impairment disorders

Synonym
Alzheimer's disease, dementia

Research involving

Human

Sponsors and support

Primary sponsor: NewAmsterdam Pharma B.V.
Source(s) of monetary or material Support: Industry (Sponsor)

Intervention

Keyword: alzheimer's disease, APOE4, cholesterol

Outcome measures

Primary outcome

The primary PD endpoint is the change from baseline in levels of ApoA-I, ApoE, small HDL particles, in both CSF as well as plasma and ABCA1-driven cholesterol efflux in CSF measured at Day 168.

Secondary outcome

1. Exploratory Pharmacodynamic Endpoints:

- Changes From Baseline Levels in Lipoproteins and Apolipoproteins in Plasma (LDL-C, TC, Non-HDL-C, TG, ApoB)
- Changes From Baseline Levels in Lipoproteins and Apolipoproteins in CSF and Plasma (HDL-C, HDL-ApoE, ApoA-II)
- Change From Baseline Levels in AD Biomarkers in CSF (p-tau 181, Ab1-42, Ab1-40, Ab1-42/Ab1-40 ratio, NfL, Neurogranin, GFAP, sTREM2, YKL40, inflammatory markers)
- Change From Baseline Levels in AD Biomarkers in Plasma (tau and p-tau epitopes, Ab1-42, Ab1-40, Ab1-42/Ab1-40 ratio, NfL)
- Correlation Between the Change From Baseline Levels in CSF p-Tau 181 and CSF

ApoA-I, ApoE, and Cholesterol Efflux Capacity

- Change From Baseline Levels in 24-Hydroxycholesterol and

27-Hydroxycholesterol in CSF and Plasma

2. Exploratory Cognition Endpoints

- Disease Progression Measured With the Cognitive-Functional Composite

- Mini-Mental State Examination

3. Exploratory Pharmacokinetic Endpoint

- Mean Plasma Levels of Obicetrapib at Steady State in CSF and Plasma

Study description

Background summary

Alzheimer*s Disease (AD), the leading cause of dementia, is a progressive, neurodegenerative disorder characterized by cognitive decline. The neuropathological hallmarks of AD are amyloid plaques consisting of fibrillar beta-amyloid (Aβ) peptides in the brain parenchyma and cerebral arteries, as well as neurofibrillary tangles consisting of aggregated hyperphosphorylated tau protein that deposit within neurons.

There is evidence to support the rationale that cholesteryl ester transfer protein (CETP) inhibition may be beneficial for AD patients. First, impaired lipid metabolism and transport is intimately associated with AD pathology, particularly with respect to apolipoprotein E (ApoE). In the brain, the ability of CETP to modulate lipoprotein composition, including ApoE lipoprotein levels, may influence lipoprotein function which may protect from cognitive decline. Second, inhibiting CETP in plasma may increase apolipoprotein A-I (ApoA-I)-containing high-density lipoprotein (HDL) particles in blood; these can transfer across the blood-brain barrier (BBB) thereby restoring brain

cholesterol transport. Third, many cardiovascular risk factors increase AD risk and large autopsy studies showed that the majority of AD brains have cerebrovascular pathologies in addition to the amyloid plaques and neurofibrillary tangles that define AD. These findings suggest that strategies such as CETP inhibition that can reduce cardiovascular risk and promote cerebrovascular resilience could potentially also reduce AD risk, particularly in the 60 to 70% of AD patients who have vascular co-morbidities and cerebrovascular pathologies.

Study objective

The primary objective of this study is to evaluate the pharmacodynamics (PD) (apolipoproteins/lipid particles and cholesterol efflux) of obicetrapib in cerebrospinal fluid (CSF) and plasma (apolipoproteins/lipid particles) in patients with early Alzheimer*s Disease (AD) (hetero/homozygote APOE4 carriers).

The exploratory objectives of this study are to evaluate:
• other PD markers of obicetrapib (additional lipoproteins, neurodegeneration, and inflammation) in patients with early AD.
• the cognitive effects of obicetrapib in patients with early AD.
• the pharmacokinetics (PK) of obicetrapib in patients with early AD

The safety objective is to evaluate the safety and tolerability of obicetrapib in patients with early AD.

Study design

This will be a proof-of-concept Phase 2a study in patients with early AD. The study is designed to assess the PD, cognitive effects, PK, and safety and tolerability of obicetrapib in early AD patients. Approximately 10 to 15 patients with early AD (hetero/homozygote APO E4 carriers) will receive obicetrapib 10 mg administered orally daily for 24 weeks.

Study duration for individual patients will approximately be 36 weeks (Screening: 1 to 8 weeks, Treatment: 24 weeks, and Follow-up: 4 weeks)

Intervention

Patients will come to the site on Day 1 (Visit 2) to begin treatment. Approximately 10 to 15 eligible patients will receive obicetrapib 10 mg once a day.
During the 24-week Treatment Period, the study drug will be administered by the patient orally and once daily on Days 1 through 168. Patients will return to the site every 6 weeks (+/- 6 days) for study assessments.

Study burden and risks

Obicetrapib has undergone extensive nonclinical testing in the standard battery of tests according to International Council for Harmonisation (ICH) guidelines, including repeat-dose toxicity studies of up to 39 weeks duration. In addition, obicetrapib has been investigated in 8 completed clinical studies, of which 6 studies were in Phase 1 of clinical development and 2 studies were in Phase 2. A total of approximately 500 subjects have been exposed to obicetrapib in these studies. In Phase 1, a total of 159 subjects received single oral doses between 5 and 150 mg of obicetrapib, and 76 subjects received consecutive doses between 1 and 25 mg of obicetrapib for periods up to 28 days. In Phase 2, a total of 268 patients received 1 to 10 mg of obicetrapib for up to 12 weeks. Single doses of obicetrapib up to 150 mg and multiple doses up to 25 mg administered over 28 days were well tolerated and safe in these studies. No clinically significant effects on vital sign measurements (systolic and diastolic blood pressure, heart rate, and body temperature), 12-lead electrocardiogram (ECG) findings, or results of safety laboratory tests or physical examinations were observed with obicetrapib treatment. In particular, no clinically significant changes in aldosterone, sodium, potassium, or bicarbonate concentrations were observed.

In contrast, the burden to potential participants is limited. It includes time spent in the study visits, discomfort during MRI and/or lumbar puncture, or adverse events due to the medication (most common are headache and nausea/vomiting).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age range: 50-75 years of age at the Screening Visit.
2. Males, or females who are post-menopausal or otherwise not of child-bearing potential.
a. Women are not considered to be of childbearing potential if they meet 1 of the following criteria as documented by the Investigator:
i. They have had a hysterectomy or tubal ligation at a minimum of 1 cycle prior to signing the ICF; or
ii. They are postmenopausal, defined as *1 year since their last menstrual period for women *55 years of age or *1 year since their last menstrual period and have a follicle stimulating hormone (FSH) level in the postmenopausal range for women <55 years of age
b. Men whose partners are of childbearing potential must agree to use an effective method of avoiding pregnancy from screening to 90 days after the last visit. Effective methods of avoiding pregnancy are contraceptive methods with a Pearl index of <1 used consistently and correctly (including implantable contraceptives, injectable contraceptives, oral contraceptives, transdermal contraceptives, intrauterine devices, diaphragm with spermicide, male or female condoms with spermicide, or cervical cap) or a sterile sexual partner;
3. Diagnosis of AD based on the NIA-AA Research Framework criteria:
Biomarker classification A+T+N+ or A+T+N- based upon:
a. CSF profile consistent with AD (an Aβ42 concentration of <1000 pg/mL AND phosphorylated tau (p-Tau) >19 pg/mL, or a ratio of p-Tau/Aβ42 of >=0.020 taken during the Screening period prior to the day of the first dose of study medication or,
b. Documented evidence of a CSF profile consistent with AD obtained within the previous 12 months, or
c. Documented amyloid positron emission tomography (PET) scan evidence acquired within the previous 12 months.
4. AD Clinical Stage 3 or 4 based on the NIA-AA Research Framework criteria
a. Have a mini-mental state examination (MMSE) score at Screening and baseline >=20.
b. Clinical Dementia Rating scale-Sum of Boxes (CDR-SB) global score >=0.5 and

<=1 with memory box score >=1.0.
5. Able to speak, read and write the local language fluently.
6. Have an APOE genotype of E4/E4 or E3/E4.
7. Patients should either be:
a. Not treated with any approved treatments for AD with a reasonable expectation that, based on the course of illness, need for treatment is not imminent and the patient should not be initiated on treatment for the length of the study, or
b. Stabilized on an approved medication(s) for the treatment of AD for at least 3 months prior to baseline. The dose of the AD treatment should remain the same after entering the study.
8. Patient and study partner are willing to consent to all study procedures.

Exclusion criteria

1. Other than AD, neurologic or medical disorder which may impair cognition including: head trauma, seizure disorder, neurodegenerative disease, hydrocephalus, cerebral/spinal hematoma, inflammatory disease, central nervous system infection (eg, encephalitis or meningitis), neoplasm, toxic exposure, metabolic disorder (including hypoxic or hypoglycemic episodes), or endocrine disorder, or any significant medical conditions that, in the opinion of the Investigator, would prohibit their participation in the study.
2. Any contra-indication to undergo magnetic resonance imaging (MRI), as judged by Investigator or radiologist.
3. MRI of the brain indicative of significant abnormality, including, but not limited to, prior hemorrhage or infarct >1 cm3, >3 lacunar infarcts, deep white matter lesions corresponding to a Fazekas score of 3, cerebral contusion, encephalomalacia, aneurysm, vascular malformation, subdural hematoma, hydrocephalus, space-occupying lesion (eg, abscess or brain tumor such as meningioma). Small incidental meningiomas may be allowed if discussed and approved by the Principal Investigator (PI).
4. History of any of the following neurological, psychiatric or medical conditions:
a. History of large vessel stroke
b. History of myocardial infarction or unstable angina within the previous 12 months
c. Type 1 diabetes and uncontrolled type 2 diabetes (hemoglobin A1c [HbA1c] >8%)
d. Systemic blood pressure >150/90 mmHg on 3 separate determinations
e. History of hyperaldosteronism
f. Significant renal or hepatic dysfunction
g. Current or previous hepatitis B infection (defined as positive test for hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody (anti-HBc). Subjects with immunity to hepatitis B (if due to natural infection defined as negative HBsAg, positive hepatitis B antibody [anti-HBs] and positive anti-HBc; if due to vaccination defined as negative HBsAg, negative

anti-HCV and positive anti-HBs) are eligible to participate in the study
h. History or positive test at Screening for hepatitis C virus antibody (anti-HCV)
i. History or positive test at Screening for human immunodeficiency virus (HIV)
j. Diagnosed with cancer with metastatic potential within the last 5 years other than carcinoma in situ of the breast or cervix, or basal cell carcinoma of the skin that has been completely excised
k. Major depressive episode requiring initiation of medication or hospitalization within the previous 90 days
l. Presence of hallucinations or delusions
m. Surgery within 12 weeks of Screening
5. Any of the following laboratory abnormalities at Screening
a. Clinically significant (as determined by a cardiologist or local PI) 12-lead ECG abnormalities
b. Any serum chemistry value (eg, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, creatine kinase [CK], total bilirubin etc) >2x the upper limit of normal (ULN) on 2 successive determinations less than 2 weeks apart
c. Serum creatinine above the ULN or estimated glomerular filtration rate (eGFR) <60 mL/min
d. Platelet count, international normalized ratio (INR), prothrombin time (PT) or partial thromboplastin time (PTT) not within the normal range or other risk for increased or uncontrolled bleeding
e. Not carrying an APOE4 allele (eg, E3/E3; E3/E2/ E2/E2).
6. Presence of contraindication to lumbar puncture as judged by local PI.
7. Any other significant medical conditions that, in the opinion of the Investigator, would prohibit participation in the study, including inability to tolerate the MRI scan or lumbar puncture procedures.
8. Taking any of the following medications
a. Antipsychotic agents, including pimavanserin
b. Stimulant medications
c. Antidepressant medications whose dose has not been stable for at least 90 days
d. Immunosuppressant medications, including chronic corticosteroids
e. Injected or infused antibody therapies, including but not limited antibodies directed against tumor necrosis factor (TNF), anti-interleukin(IL)-6, natalizumab, rituximab and similar agents
f. Anticoagulant or anti-platelet medications including warfarin, heparanoids and direct coagulation factor inhibitors (eg, apixaban, dagibatran, rivaroxaban); either aspirin at a dose of <=100 mg/day or clopidogrel at a dose of 75 mg/day, but not both in combination is permitted.
g. Any lipid-altering therapies
9. Participation in any other interventional clinical trial, or treatment with any investigational drug or investigational use of an approved therapy within 30 days (or 5 half-lives of such agent) prior to the first Screening visit.
10. Regular use of cannabis or cannabis products, including non-prescription products containing cannabidiol.

11. History of drug (including cannabis) or alcohol abuse within the last 5 years.
12. Known CETP inhibitor allergy or intolerance.
13. Has an active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
a. Note: A subject being screened for this study who had a documented, positive polymerase chain reaction (PCR) or serology test for SARS-CoV-2 may be enrolled provided the subject has:
i. Recovered from COVID-19 ie, all COVID-19 related symptoms and major clinical findings which could potentially affect the safety of the subject should be resolved to baseline, and
ii. A negative result from a health authority-authorized nucleic acid amplification (PCR) test for SARS-CoV-2 taken.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-01-2022
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	obicetrapib
Generic name:	obicetrapib

Ethics review

Approved WMO Date:	09-08-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-002687-41-NL
CCMO	NL77871.029.21

Study results

Date completed:	01-06-2023
Results posted:	30-05-2024

First publication
15-05-2024