CLINICAL STUDY PROTOCOL

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)

Investigational Product: Obicetrapib
Protocol Number: TA-8995 AD-1
EudraCT Number: 2021-002687-41

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V1.0	16 June 2021
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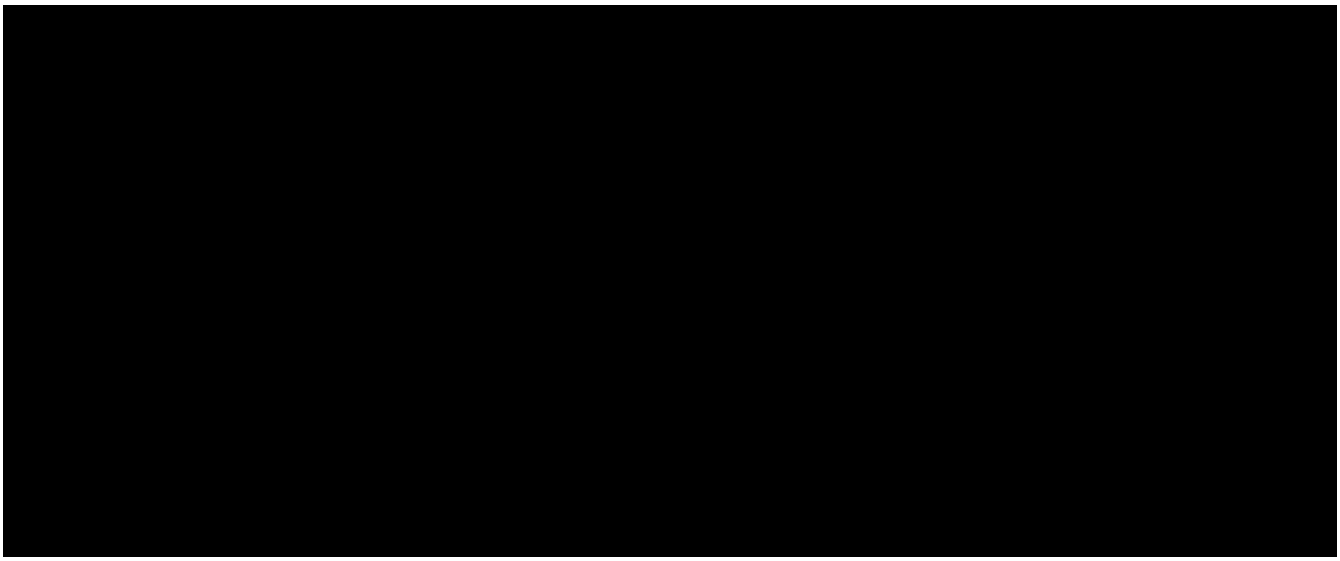
SIGNATURE PAGE

STUDY TITLE: 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)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.



INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provisions of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by NewAmsterdam Pharma BV to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to NewAmsterdam Pharma BV and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by NewAmsterdam Pharma BV, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Ethics Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

SYNOPSIS

TITLE: 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)

PROTOCOL NUMBER: TA-8995 AD-1

INVESTIGATIONAL PRODUCT: Obicetrapib

PHASE: 2a

INDICATION: early Alzheimer's disease

OBJECTIVES: 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 of this study is to evaluate the safety and tolerability of obicetrapib in patients with early AD.

POPULATION: The population for this study includes men and women, 50 to 75 years of age at Screening, with a clinical diagnosis of AD Stage 3 or 4 based on the National Institute on Aging-Alzheimer's Association (NIA-AA) Research Framework criteria. Patients must have an APOE genotype of E4/E4 or E3/E4.

STUDY DESIGN AND DURATION: This study will be a proof of concept, Phase 2a study in patients with early AD to evaluate the PD, cognitive effects, PK, and safety and tolerability of obicetrapib therapy. Study duration for individual patients will approximately be 36 weeks (Screening: 1 to 8 weeks, Treatment: 24 weeks, and Follow-up: 4 weeks).

Screening Period

At the Screening Visit, patients and their study partners will be required to sign an informed consent form (ICF) before any study-related procedures are performed. After signing the ICF, patients will be assessed for study eligibility.

Treatment Period

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.

Safety Follow-up Period

Patients will be contacted by phone for a Safety Follow-up Visit (Visit 7) approximately 4 weeks (+/- 6 days) after the end of the Treatment Period for collection of AEs.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION: The study drug will consist of 5 mg obicetrapib tablets.

Two tablets of study drug (10 mg in total) will be administered by the patient orally and once daily on Day 1 to Day 168 at approximately the same time each morning.

PHARMACOKINETIC AND PHARMACODYNAMIC VARIABLES: The primary PD endpoint is the change from baseline in levels of apolipoprotein A-I (ApoA-I), apolipoprotein E (ApoE), small high-density lipoprotein (HDL) particles, in both CSF as well as plasma and ABCA1-driven cholesterol efflux in CSF measured at Day 168.

The exploratory PD endpoints include the following:

- Changes from baseline levels in plasma of low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), non-high-density lipoprotein-cholesterol (non-HDL-C), triglycerides (TG), and apolipoprotein B (ApoB)
- Changes from baseline levels in CSF and plasma of high-density lipoprotein cholesterol (HDL-C), HDL-ApoE, and apolipoprotein A-II (ApoA-II)
- AD Biomarkers:
    - Change from baseline levels in CSF of:
        - Tau and phosphorylated tau at Thr181 (p-Tau 181)
        - $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio
        - Neurogranin
        - Neurofilament light
        - Glial fibrillary acidic protein (GFAP)
        - sTREM2
        - YKL40
        - Inflammatory markers (eg, interferon [IFN]-γ, interleukin[IL]-10, IL-12p70, IL-17A, IL-6, tumor necrosis factor [TNF]-α)
    - Change from baseline levels in plasma of
        - Tau and p-Tau epitopes
        - $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio
        - Neurofilament light
- 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

The exploratory cognition endpoints include the following:

- Disease progression measured with the Cognitive-Functional Composite (CFC)
- Mini-mental state examination (MMSE)

The exploratory PK endpoint is mean plasma levels of obicetrapib at steady state in CSF and plasma

SAFETY VARIABLES: The safety and tolerability profile of obicetrapib will be assessed by:

- Incidences of adverse events (AEs) and serious adverse events (SAEs)
- Change from baseline in clinical laboratory results (chemistry, hematology and urinalysis), vital signs, physical and neurological examination findings, and electrocardiogram (ECG).

STATISTICAL ANALYSES: All study-collected data will be summarized using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include number of patients (n), mean, standard deviation (SD), median, minimum, and maximum values. Analysis of categorical variables will include frequency and percentage.

Analysis of Safety

The Safety Population will include all patients who receive at least 1 dose of study drug. The Safety Population will be the primary population used for the safety analyses. All safety endpoints will be summarized descriptively. No statistical inference will be applied to the safety endpoints.

Analysis of PD, effects on cognition, and PK

The Intent-to-Treat (ITT) Population will include all patients who receive at least 1 dose of study drug.

The Per-Protocol (PP) Population will include all patients who have a study drug compliance percentage of at least 80% over the entire study duration.

The PP Population will be the primary population used for the PD and PK analyses, and for the analyses of the effects of obicetrapib on cognition. The PD, PK, and effects of obicetrapib on cognition will also be analyzed using the ITT Population as supportive analysis.

The primary PD endpoint, as well as all exploratory endpoints will be summarized descriptively. No statistical inference will be applied to the primary PD endpoint and the exploratory endpoints.

SAMPLE SIZE DETERMINATION: No formal sample size determination was performed. A total number of 10 to 15 patients is considered sufficient for this proof-of-concept study.

SITES: Brain Research Center Amsterdam, the Netherlands and potentially one or 2 additional sites in the Netherlands.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
Aβ	Beta-amyloid
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive
AE	Adverse event
A-IADL-Q-SV	Amsterdam Instrumental Activities of Daily Living Questionnaire
ALT	Alanine aminotransferase
Anti-HB	Hepatitis B antibody
Anti-HBc	Hepatitis B core antibody
Anti-HCV	Hepatitis C virus antibody
ApoA-I	Apolipoprotein A-I
ApoA-II	Apolipoprotein A-II
ApoB	Apolipoprotein B
ApoE	Apolipoprotein E
ApoE4	Apolipoprotein E4
AST	Aspartate aminotransferase
BBB	Blood-brain barrier
CDR	Clinical Dementia Rating Scale
CETP	Cholesteryl ester transfer protein
CFC	Cognitive-Functional Composite
CK	Creatine kinase
COVID-19	Coronavirus disease 2019
CSF	Cerebrospinal fluid
CTA	Clinical trial authorisation
ECG	Electrocardiogram
EOT	End of treatment
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EIU	Exposure In Utero
GCP	Good Clinical Practice
GFAP	Glial fibrillary acidic protein
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
ICF	Informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
INR	International normalized ratio
ITT	Intent-to-Treat
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
NIA-AA	National Institute on Aging-Alzheimer's Association
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PET	Positron emission tomography
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol
PT	Prothrombin time
p-Tau	Phosphorylated tau
PTT	Partial thromboplastin time
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T4	Thyroxine
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TNF	Tumor necrosis factor
TSH	Thyroid stimulation hormone
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein
WMO	Wet medisch-wetenschappelijk onderzoek met mensen (Dutch)

1 INTRODUCTION AND BACKGROUND INFORMATION

Cholesteryl Ester Transfer Protein Inhibition and Alzheimer's Disease

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)[1]. 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[2]. 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. Fourth, AD has a long prodromal period as neuropathological changes begin to occur 15 to 20 years prior to clinical onset of memory problems that typically emerge in the 6th and 7th decade of life[3]. This provides a relatively large window of opportunity for both primary and secondary prevention strategies based on evaluation of genetic factors and biomarker levels that could select individuals at risk for AD who are most likely to benefit from CETP inhibition.

CETP is a plasma glycoprotein produced in the liver and adipose tissue. It circulates in the blood bound primarily to HDL cholesterol (HDL-C) and is involved in the transfer of cholesteryl esters and triglycerides (TG) between lipoproteins. In particular, it mediates the transfer of cholesteryl esters from HDL to the apolipoprotein B (ApoB)-containing particles, very low-density lipoprotein (VLDL) and low-density lipoprotein cholesterol (LDL-C), in exchange for TG. Cholesteryl esters from HDL can be taken up by the liver through scavenger receptor class B type 1; this action also leads to decreased HDL-C levels and ultimately to increased LDL-C levels.

Inhibition of CETP activity increases levels of particular subfractions of plasma HDL, including both ApoA-I and ApoE containing HDL[4,5,6]. Circulating HDL has multiple vaso-protective functions including stimulating reverse cholesterol transport, reducing endothelial activation, and mitigating endothelial inflammation[7,8]. HDL has been extensively studied in cardiovascular disease[9,10] and recent studies suggest a potential role in AD[7,8]. High levels of HDL-C or ApoA-I (HDL's major protein) correlate with reduced AD risk[11], improved memory[12,13], and low brain amyloid[14].

The APOE gene is by far the most significant genetic risk factor for sporadic late onset AD, with allele E2 (Cys112, Cys158) being protective, allele E3 (Cys112, Arg158) being neutral, and allele E4 (Arg112, Arg158) being detrimental[15]. The mechanisms by which ApoE affects AD risk and age of onset remain incompletely understood. The best-studied effect of apolipoprotein E4

(ApoE4) is accelerated amyloid deposition due to impaired Aβ clearance[16,17]. Aβ is cleared from the brain by direct transport across the BBB[16,17,18,19,20] and via perivascular drainage in mid- and large-sized arteries along smooth muscle cell basement membranes[21]. Disrupted Aβ clearance leads to amyloid deposition and further amyloid pathology. Furthermore, disrupted brain cholesterol transport by ApoE4 has been shown to increase neuronal cholesterol and cholesterol esters, leading to AD pathology in an amyloid-independent manner[22].

In the brain, ApoE is secreted mainly from astrocytes, microglia, and pericytes, and circulates in cerebrospinal fluid (CSF) on lipoprotein particles that resemble plasma HDL[23]. Until very recently, only the pool of brain derived ApoE was considered important for AD as peripheral ApoE that is secreted from hepatocytes and macrophages does not cross the BBB[24]. However, clinical, animal model, and *in vitro* studies are now challenging this view and demonstrate that peripheral ApoE, especially on HDL that may be particularly amenable to CETP inhibition, may have a larger impact on brain health than previously recognized[25,26].

In summary, there is ample rationale to believe that increasing HDL-C, HDL-ApoE and HDL-ApoA-I in both plasma and brain through CETP inhibition could ameliorate AD pathology. Inhibition of CETP might therefore be a potentially therapeutic intervention in AD patients that could prevent or delay cognitive decline and finally dementia.

Obicetrapib

Obicetrapib has been shown to be a selective CETP inhibitor. In addition to shuttling cholesterol esters from LDL-C to HDL-C particles, obicetrapib has several additional compound-specific activities that are hypothesized to be beneficial in patients. Obicetrapib treatment has recently been shown to reduce the number of ApoB-containing particles that constitute LDL-C. Obicetrapib increases ApoE, which leads to removal of cholesterol via the liver and also reduces lipoprotein (a) (Lp(a)). Finally, obicetrapib not only potently increases HDL-C and the number of ApoA-I containing lipoproteins but has been demonstrated to be a potent inducer of cholesterol efflux, which is the main driver of reverse cholesterol transport. This effect is considered important because it is expected to reduce established atheroma burden[27].

Clinical Development of Obicetrapib

Both single ascending dose (TA-8995-01) and multiple ascending dose (TA-8995-02) studies have been conducted in healthy volunteers. A formal thorough QT/QTc study (TA-8995-04) has been completed and obicetrapib was shown to have no effect on corrected QT interval by Fridericia (QTcF). A drug-drug interaction study (TA-8995-05) has also been conducted; this study showed no significant effect of obicetrapib on P-glycoprotein activity, but this study showed that obicetrapib is a mild inducer of cytochrome P450 3A4. A mass balance study in healthy males concluded that obicetrapib is steadily absorbed, and the principal route of excretion was in the feces (TA-8995-07). Finally, bioequivalence between obicetrapib capsule and tablet formulations was investigated (TA-8995-08) and established.

The first patient study conducted was a Phase 2 clinical study (TA-8995-03) in Denmark and the Netherlands where the aim was to evaluate the optimal dose of obicetrapib alone and in combination with statins in patients with mild dyslipidemia. The 10 mg dose of obicetrapib reduced LDL-C by 45 % and ApoB levels by 33.7%, respectively, compared to baseline. In addition, the 10 mg dose was the most efficacious dose to increase HDL associated lipoproteins and cholesterol efflux parameters. HDL-C levels increased by 179%, while ApoA-I levels were

increased by 63.4%. Significant increases of total, non-ABCA1-, and ABCA1- specific cholesterol efflux capacity by 38%, 72%, and 28%, respectively, were observed. Finally, preBeta-1 HDL, a small discoidal lipid-poor particle that is the primary acceptor for ABCA1-driven cholesterol efflux, was significantly increased by 36% for obicetrapib 10 mg monotherapy. Obicetrapib was well tolerated and no safety issues were observed[28]. A second patient study (TA-8995-06) was conducted where the effect of obicetrapib on Lp(a) was investigated following 12 weeks of treatment. There was a statistically significant reduction in Lp(a) levels following 12 weeks of treatment.

The 10 mg dose was chosen for this proof-of-concept study because of the efficacy results observed with the obicetrapib 10 mg dose, especially in the lipoprotein parameters of interest, combined with the good tolerability.

Risk/Benefit

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.

Obicetrapib has been shown to be a selective CETP inhibitor. In addition to shuttling cholesterol esters from LDL-C to HDL-C particles, obicetrapib has several additional compound-specific activities that are hypothesized to be beneficial in patients. A dose of 5 mg obicetrapib resulted in an LDL-C reduction of 45.3%, an ApoB reduction of 33.6%, an HDL-C increase of 157.1%, an ApoA-I increase of 57.5%, and a significant increase in HDL-C efflux capacity[28]. This effect is considered important because it is expected to reduce established atheroma burden.

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 addition, no dose-related effects have been observed on the type, frequency, or intensity of treatment-emergent adverse events (TEAEs) in clinical studies of obicetrapib to date. In patient studies, most TEAEs were mild or moderate in severity. Of the patients with severe TEAEs, 2 were suspected to be related to both obicetrapib and concomitant statin treatment. The number of patients experiencing TEAEs and their severity were similar across all treatment groups. Incidence rates of drug-related TEAEs were also comparable for all treatment groups; the number of TEAEs in the obicetrapib treatment groups did not display a dose-dependent effect. There were 7 randomized patients with a treatment-emergent serious adverse event (SAE), none of which were suspected to be study drug related. One patient had treatment-emergent SAEs that resulted in study discontinuation. No deaths occurred during these studies.

2 STUDY OBJECTIVES

Primary 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).

Exploratory Objectives

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.

Safety Objective

- To evaluate the safety and tolerability of obicetrapib in patients with early AD.

3 STUDY DESCRIPTION

Summary of 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.

The study is intended to take place at a single site: the Brain Research Center, Amsterdam, the Netherlands. However, 1 or 2 sites in the Netherlands could be added.

The population for this study includes men and women, 50 to 75 years of age at Screening, with a clinical diagnosis of AD Stage 3 or 4 based on the National Institute on Aging-Alzheimer's Association (NIA-AA) Research Framework criteria. Patients must have an APOE genotype of E4/E4 or E3/E4.

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

3.1.1 Screening Period

At the Screening Visit, patients and their study partners will be required to sign an informed consent form (ICF) before any study-related procedures are performed. After signing the ICF, patients will be assessed for study eligibility.

3.1.2 Treatment Period

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.

3.1.3 Safety Follow-up Period

Patients will be contacted by phone for a Safety Follow-up Visit (Visit 7) approximately 4 weeks (+/- 6 days) after the end of the Treatment Period for collection of adverse events (AEs).

Study Indication

The indication for this study is early AD.

Coronavirus Disease 2019 Contingency Measures

In cases of coronavirus disease 2019 (COVID-19) limitations, it is the Investigator's responsibility to assure the safety of patients, including phone or video contact to assess the patient's well-being including any AE, collection of study samples, and clinical data as best as possible, and direct shipment of study drug to the patient, if necessary. Where available and appropriate, home health care may be considered to facilitate monitoring of safety and study continuity. Documentation of these cases and the study site's management of patients should be recorded in the Investigator

study files. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

4 SELECTION AND WITHDRAWAL OF PATIENTS

Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

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. Clinical Dementia Rating scale global score ≥0.5 and ≤1
    b. Mini-mental state examination (MMSE) score at Screening and baseline ≥20
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

Patients who meet any of the following criteria will be excluded from participation in the study:

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 cm^3, >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, heparinoids 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 pharmacologic agent known to significantly induce or inhibit drug-metabolizing enzymes (especially inducers and inhibitors of CYP3A4 and CYP2C9) within 30 days before initial dosing

h. 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.

Retesting

If laboratory abnormalities during Screening are considered by the Investigator to be transient, then the laboratory tests may be repeated once during Screening. The Investigator's rationale for retesting should be documented. If the retest result is no longer exclusionary, the patient may be enrolled.

Rescreening

Patients who have screen-failed are permitted to rescreen once, following consultation with the Medical Monitor. Rescreening may be scheduled after at least 5 days have elapsed from the previous study visit.

Withdrawal Criteria

Participation in this clinical study may be discontinued for any of the following reasons:

- The patient and or study partner withdraws consent or requests discontinuation from the study for any reason;
  - However, if the patients wants to stay in the trial despite the discontinuation of the study partner, the patient is able to appoint another study partner in order to stay in the trial.
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;

- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Pregnancy;
- Requirement of prohibited concomitant medication;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

If a patient withdraws prematurely from the study due to any of the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination Visit. The reason for patient withdrawal must be documented in the electronic case report form (eCRF). The patient is not obligated to undergo the full panel of assessments scheduled for the Early Termination Visit if he/she does not wish to.

In the case of patients lost to follow-up, at least 3 attempts to contact the patient must be made and documented in the patient's medical records.

Withdrawn patients will not be replaced.

5 STUDY TREATMENTS

Treatment Groups

Patients will be treated with obicetrapib 10 mg.

Rationale for Dosing

In previous multiple-dose clinical studies of obicetrapib in healthy subjects and patients, maximal effects associated with the hypothesized benefit of obicetrapib in AD patients were observed with the 10 mg obicetrapib dose. At this dose level, CETP activity and concentrations were effectively reduced, and HDL-C as well as ApoA-I and ApoE levels were maximally increased while LDL-C levels decreased.

Randomization and Blinding

Patients who meet all eligibility criteria will be enrolled into the study. All patients will be treated with obicetrapib 10 mg.

Breaking the Blind

Not applicable, the study will be conducted in an open-label fashion.

Drug Supplies

5.1.1 Formulation and Packaging

The study drug will consist of 5 mg obicetrapib tablets. All products are manufactured in accordance with current European Union Good Manufacturing Practice.

Obicetrapib tablets are round, white film-coated tablets, with no identifying markings, containing 5 mg of obicetrapib calcium drug substance. [redacted]

Obicetrapib tablets will be packaged into foil blisters and assembled into wallet cards. The wallet cards will be clearly labelled to indicate which blisters to use on each day. wallet cards will be assembled into kits, and each kit will provide a sufficient supply for 6 weeks of dosing. The shelf-life will be assigned based on the stability of the individual products. The kits should be stored below 25°C.

The physical, chemical, and pharmaceutical formulation properties and characteristics of the obicetrapib tablets are described in the Investigator's Brochure.

Study drug will be labelled in accordance with all applicable local regulatory requirements.

5.1.2 Study Drug Preparation and Dispensing

The study drug used in this study will consist of 5 mg obicetrapib tablets.

At each appropriate visit (Visits 2, 3, 4, and 5), patients will receive a kit containing wallet cards with the study drug. Patients will be instructed to take 2 tablets from the wallet cards in the kit each day. The wallet cards will be clearly labelled to indicate which blisters to use on each day.

Each kit will provide a sufficient supply for 6 weeks of dosing. Patients will be instructed to return all used and unused study drug at the next visit.

This study protocol includes contingency measures to manage disruptions due to COVID-19 control measures, including modifications to study drug dispensation specific to situations where COVID-19 is impacting study conduct. See Section 3.3 for details of COVID-19 contingency measures. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

5.1.3 Study Drug Administration

Study drug will be administered by the patient orally and once daily on Days 1 through 168. Study drug should be administered at approximately the same time each morning. If a patient forgets to take study drug on a given day, they should take the next dose as normal and should not take a double dose to make up for the forgotten dose.

5.1.4 Treatment Compliance

Compliance to the study drug regimen will be evaluated by counting unused tablets and capsules. During the Treatment Period, if compliance is not between 80% and 120%, inclusive, the patient will be counselled about the importance of compliance to the regimen. If the limits are exceeded at 2 consecutive visits, a decision will be made by the Investigator and Sponsor as to whether the patient should be withdrawn from the study.

5.1.5 Storage and Accountability

Study drug must be stored below 25°C in a secure area with access limited to the Investigator and authorized site personnel.

In accordance with regulatory requirements, the Investigator or designated site personnel must document the amount of study drug dispensed and/or administered to patients, the amount returned by patients, and the amount received from and returned to the Sponsor (or representative) when applicable. Study drug accountability records must be maintained throughout the course of the study. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study drug will be provided in the appropriate study manual.

Prior and Concomitant Medications and/or Procedures

5.1.6 Excluded Medications and/or Procedures

Subjects who are using any of the following medications will be excluded from participation in the study (see Section 4.2):

- Antipsychotic agents, including pimavanserin;
- Stimulant medications;
- Antidepressant medications whose dose has not been stable for at least 90 days;
- Immunosuppressant medications, including chronic corticosteroids;
- Injected or infused antibody therapies, including but not limited antibodies directed against TNF, anti-IL-6, natalizumab, rituximab and similar agents;

- Anticoagulant or anti-platelet medications including warfarin, heparinoids 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;
- Any lipid-altering therapy other than the investigational study drug.

5.1.7 Documentation of Prior and Concomitant Medication Use

Medications used within 28 days prior to the Screening Visit will be recorded. Any medications administered in addition to the study drug, whether allowed per the protocol or not, must be documented on the concomitant medication eCRF.

6 STUDY PROCEDURES

A study visit schedule in tabular format is provided in Appendix A. This study protocol includes contingency measures to manage disruptions due to COVID-19 control measures, including modifications to visit schedules and procedures specific to situations where COVID-19 is impacting study conduct. See Section 3.3 for details of COVID-19 contingency measures. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

Screening Visit (Visit 1, Week -8 to Day -1)

Patients who the Investigator considers to be appropriate for the study, will have the study explained to them and their study partner by the Investigator and will be given a dedicated copy of the written ICF. When they have had sufficient time to study this information and the opportunity to ask any questions they wish, they will be invited to give their consent to participation by signing the ICF. Signed informed consent must be obtained before any study-related procedures are performed. See Section 11.4 for details on informed consent.

Once the patients and their study partners have given consent, the following procedures will be undertaken to confirm eligibility for the study:

- Verification of inclusion and exclusion criteria;
- Confirmation of diagnosis of Stage 3 or 4 AD per NIA-AA Research Framework criteria (see Section 4.1);
  - CDR global score between ≥0.5 and ≤1
  - MMSE score of ≥ 20
- Blood sampling for APOE E4 genotyping;
- Performing MRI of cerebrum (only in patients without historical MRI available within 6 months of the Screening Visit);
- Documentation of demographics, medical history and baseline conditions;
- Recording of height and weight;
- Recording of vital signs (body temperature, heart rate, and triplicate blood pressure [systolic and diastolic]);
- Performing 12-lead ECG;
- Fasting (~10 hours) blood sampling for hematology and clinical chemistry

  Note: HbA1c, thyroid stimulation hormone (TSH), triiodothyronine (T3), thyroxine (T4), folic acid, and vitamin B12 levels will be determined at Screening Visit only.
- Collection of urine sample for urinalysis;
- FSH and urine pregnancy test for women <55 years of age
- Physical and neurological examination;
- Documentation of prior and concomitant medication; and

- Performing of lumbar puncture for CSF sample (for inclusion and PD and PK parameters as listed in Section 7).

The MMSE must be performed at least 14 days prior to the MMSE performed at the Baseline visit to minimize learning effects.

The CDR test was designed for the staging of dementia severity. It is a 5-point scale used to characterize six domains of cognitive and functional performance applicable to AD and related dementias: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. The necessary information to make each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (eg, family member) referred to as the CDR Assessment Protocol.

Each area is rated as 0 (“healthy”), 0.5 (“questionable dementia”), 1 (“mild dementia”), 2 (“moderate dementia”), or 3 (“severe dementia”).

CDR ≥0.5 and ≤1 (in combination with MMSE ≥ 20) covers the same clinical stage in the Alzheimer’s continuum as described in AD Clinical Stage 3 or 4 in the NIA-AA Research Framework.

The Screening Visit may be divided into multiple visits if more convenient for the participant.

Treatment Period – Visits 2 Through 5

6.1.1 Baseline Visit (Visit 2, Day 1)

The following procedures will be performed at Baseline (Visit 2, Day 1):

- Confirmation that the patient continues to meet the inclusion and exclusion criteria and assessing any updates since the Screening Visit;
- Recording of vital signs;
- Documentation of prior and concomitant medications;
- Documentation of AEs;
- Physical and neurological examination
- Administration of the Columbia-Suicide Severity Rating Scale (C-SSRS);
- Administration of Cognitive-Functional Composite (CFC) and MMSE;
- Fasting (~10 hours) blood sampling for clinical chemistry, and PD and PK parameters as listed in Section 7;

Patients will receive a supply of study drug with instructions on how to take it. Patients will be given an appointment to return with all used and unused study drug at Day 42 (±6 days).

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicidality assessment. The scale will be used to determine treatment-emergent suicidal ideation and behavior.

6.1.2 Visit 3 (Day 42 ±6 Days)

All patients returning for Visit 3 (Day 42 ±6 days) will undergo the following procedures:

- Fasting (~10 hours) blood sampling for clinical chemistry and hematology;
- Recording of vital signs;
- Administration of the Columbia-Suicide Severity Rating Scale (C-SSRS);
- Documentation of AEs and concomitant medications;
- Study drug compliance check; and

Patients will receive a supply of study drug with instructions on how to take it. Patients will be given an appointment to return with all used and unused study drug at Day 84 (±6 days).

6.1.3 Visit 4 (Day 84 ±6 Days)

All patients returning for Visit 4 (Day 84 ±6 days) will undergo the following procedures:

- Recording of vital signs;
- Physical and neurological examination;
- Documentation of AEs and concomitant medications;
- Administration of the Columbia-Suicide Severity Rating Scale (C-SSRS);
- Administration of MMSE;
- Fasting (~10 hours) blood sampling for clinical chemistry and PD and PK parameters (see Section 7).
- Optional: performing of lumbar puncture for CSF sample (see Section 7);
- Study drug compliance check; and

Patients will receive a supply of study drug with instructions on how to take it. Patients will be given an appointment to return with all used and unused study drug at Day 126 (±6 days).

6.1.4 Visit 5 (Day 126 ±6 Days)

All patients returning for Visit 5 (Day 126 ±6 days) will undergo the following procedures:

- Fasting (~10 hours) blood sampling for clinical chemistry and hematology;
- Recording of vital signs;
- Administration of the Columbia-Suicide Severity Rating Scale (C-SSRS);
- Documentation of AEs and concomitant medications;
- Study drug compliance check; and

Patients will receive a supply of study drug with instructions on how to take it. Patients will be given an appointment to return with all used and unused study drug at Day 168 (±6 days).

6.1.5 End of Treatment Visit 6 (Day 168 ±6 Days)

All patients returning for Visit 6 (Day 168 ±6 days) will undergo the following procedures:

- Recording of weight;
- Recording of vital signs;
- Performing 12-lead ECG;
- Fasting (~10 hours) blood sampling for hematology, clinical chemistry, and PD and PK parameters (see Sections 7 and 8.7);
- Collection of urine sample for urinalysis;
- Physical and neurological examination;
- Documentation of AEs and concomitant medication;
- Administration of the Columbia-Suicide Severity Rating Scale (C-SSRS);
- Administration of MMSE and CFC;
- Performing of lumbar puncture for CSF sample; and
- Study drug compliance check

6.1.6 End of Study Visit 7 (Day 198 ±6 Days)

Patients will be contacted by phone for a safety follow-up (Visit 7) approximately 4 weeks (±6 days) after the End of the Treatment Visit (Visit 6) for collection of AEs.

Early Termination Visit and Withdrawal Procedures

The end of the study for patients completing the study is Visit 7. For patients who are withdrawn from the study prior to completion, all procedures planned to be performed at the End of Treatment (EOT) Visit (Visit 6) will be conducted at an Early Termination Visit if possible.

7 PHARMACODYNAMIC AND PHARMACOKINETIC ASSESSMENTS

Blood samples for lipoproteins and apolipoproteins must be obtained under fasting conditions (ie, after the patient has fasted for ~10 hours). For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. If a patient is not fasted, the Investigator will reschedule the visit as soon as possible.

Primary Pharmacodynamic Endpoint

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.

Exploratory Pharmacodynamic Endpoints

Exploratory analyses may be performed to further investigate the PD of obicetrapib. These may include, but might not be limited to, the following assays at selected time points:

Changes From Baseline Levels in Lipoproteins and Apolipoproteins in Plasma
At Baseline (Visit 2), at Day 84 (Visit 4), and the End of Treatment (Day 168, Visit 6), the following parameters will be measured:

- LDL-C
- Total cholesterol (TC)
- Non-HDL-C
- TG
- ApoB

Changes From Baseline Levels in Lipoproteins and Apolipoproteins in CSF and Plasma
At Screening (Visit 1) or Baseline (Visit 2), at Day 84 (Visit 4), and at the End of Treatment (Day 168, Visit 6), the following parameters will be measured:

- HDL-C
- HDL-ApoE
- Apolipoprotein A-II (ApoA-II)

Note, baseline levels of CSF lipoproteins and apolipoproteins will be determined at Screening (Visit 1) since CSF sampling is required for inclusion. Baseline levels of plasma lipoproteins and apolipoproteins will be determined at Baseline (Visit 2). CSF sampling for CSF lipoproteins and apolipoproteins at Day 84 (Visit 4) is optional.

Change From Baseline Levels in AD Biomarkers in CSF
At Screening (Visit 1), at Day 84 (Visit 4), and at the End of Treatment (Day 168, Visit 6), the following parameters will be measured in the CSF:

- Tau and phosphorylated tau at Thr181 (p-Tau 181)
- $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio
- Neurogranin
- Neurofilament light
- Glial fibrillary acidic protein (GFAP)
- sTREM2
- YKL40

- Inflammatory markers (eg, interferon [IFN]-γ, IL-10, IL-12p70, IL-17A, IL-6, TNF-α)

Note, CSF sampling for AD biomarkers in CSF at Day 84 (Visit 4) is optional.

Change From Baseline Levels in AD Biomarkers in Plasma
At Baseline (Visit 2), at Day 84 (Visit 4), and the End of Treatment (Day 168, Visit 6), the following parameters will be measured in the plasma:

- Tau and p-Tau epitopes
- $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio
- Neurofilament light

Correlation Between the Change From Baseline Levels in CSF p-Tau 181 and CSF ApoA-I, ApoE, and Cholesterol Efflux Capacity
At Screening (Visit 1) and at the End of Treatment (Day 168, Visit 6), p-Tau 181, ApoA-I, ApoE, and cholesterol efflux capacity will be measured in the CSF.

Change From Baseline Levels in 24-Hydroxycholesterol and 27-Hydroxycholesterol in CSF and Plasma
At Baseline (Visit 2), Day 84 (Visit 4), and the End of Treatment (Day 168, Visit 6), 24-hydroxycholesterol and 27-hydroxycholesterol will be measured in the CSF and plasma samples.

Note, CSF sampling for 24-hydroxycholesterol and 27-hydroxycholesterol in CSF at Day 84 (Visit 4) is optional.

Exploratory Cognition Endpoints

Disease Progression Measured With the Cognitive-Functional Composite

At Baseline (Visit 2) and the End of Treatment (Day 168, Visit 6), the CFC test will be administered to allow tracking of disease progression.

The CFC test was designed to improve the measurement of progression in early dementia stages of AD by providing a short and clinically relevant measure focusing on the cognitive domains and activities of daily living that are sensitive to decline in early AD.

The CFC combines the Short Version of the Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q-SV) and a brief neuropsychological test battery focusing on episodic memory and executive functions[29,30]. The psychometric quality of the CFC was evaluated in the Catch-Cog study; an international, multi-center, independent longitudinal validation study including individuals with MCI and mild dementia due to AD[29]. The CFC was found to have good test-rest reliability, and patients and caregivers experienced the content of the CFC as relevant and the administration as user-friendly[30,31]. Further, it was shown that the CFC has good construct validity and quality for the target population, as evidenced by associations with clinical and biological measures of disease severity[32,33], and limited range restrictions in scoring at baseline[33].

The cognitive component includes seven existing cognitive tests that are administered by a trained rater (duration: 20-25 minutes). The A-IADL-Q-SV measures 30 cognitively complex instrumental activities of daily living, and is completed independently by the study partner on a tablet computer (duration: 10-15 minutes). The seven existing cognitive tests include the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) Word Recognition, the

ADAS-Cog Orientation, the ADAS-Cog Word Recall, the Digit Span Backward Task, the Controlled Oral Word Association Test, the Category Fluency Test, and the Digit Symbol Substitution Test.

Mini-Mental State Examination

At Screening (Visit 1), Baseline (Visit 2), Day 84 (Visit 4), and the End of Treatment (Day 168, Visit 6), the MMSE will be administered.

The MMSE is a cognitive screening test originally designed for the grading of dementia severity. The MMSE test can be performed in approximately 5 to 10 minutes. The MMSE assesses different aspects of cognition: orientation, registration, attention and calculation, recall, language, repetition, and complex commands.

MMSE scores range from 0 to 30, with a score of 24 or higher indicating normal cognition.

Exploratory Pharmacokinetic Endpoint

Mean Plasma Levels of Obicetrapib at Steady State in CSF and Plasma
At Screening obicetrapib concentrations will be measured in the CSF. At Day 1 (Visit 2) obicetrapib concentrations will be measured in plasma. At Day 84 (Visit 4) and the End of Treatment (Day 168, Visit 6), obicetrapib concentrations will be measured in the CSF and plasma samples.

8 SAFETY ASSESSMENTS

Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of first dose of study drug until the end of the study. Patients or their study partner should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study drug. Beginning at the date of the first dose of study drug, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at the date of the first dose of study drug should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline change in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination findings that are detected during the study or are present at the date of the first dose of study drug and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings should be reported as an AE based on the clinical judgment of the Investigator.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For obicetrapib, the reference

safety information is included in the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of yes or no.

Assessment of Severity

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality Assessment

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, or unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, or respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of the first dose of study drug until 30 days following the last administration of study drug must be reported to [redacted] within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator

considers related to study drug must be reported to [redacted] or the Sponsor/designee.

To report the SAE, complete the paper SAE report form and forward the form by fax or email to [redacted] at [redacted] or call the [redacted] SAE reporting line (phone number listed below), within 24 hours of awareness. Simultaneously, the investigator must record the SAE and any additional information on the relevant source documentation/eCRF, as appropriate.

The Sponsor/designee or Investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited IEC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the Sponsor/designee or Investigator has first knowledge of the serious adverse events.

Safety Contact Information: [redacted]
[redacted] SAE reporting line – Europe:
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

Follow-up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the paper SAE form and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to [redacted] via fax or email. Simultaneously, the investigator must record the updates and any additional information on the relevant source documentation/eCRF, as appropriate.

Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to [redacted] within 24 hours of knowledge of the event. [redacted] will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to [redacted]

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify [redacted] as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to

[redacted] If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the applicable competent authorities in all the Member States concerned and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the applicable competent authorities concerned and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of patients missing doses of investigational product are not considered reportable as medication errors.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations report form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the special situations report form and faxed/emailed to [redacted] contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these special situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: [redacted]
[redacted] SAE reporting line – Europe:
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

Clinical Laboratory Evaluations

Blood for chemistry and hematology will be obtained as indicated in Appendix A and sent to a central laboratory for analysis. See Appendix B for a complete list of analytes. Blood samples for chemistry and hematology must be obtained under fasting conditions (ie, after the patient has fasted for ~10 hours). For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. If a patient is not fasting, the Investigator will reschedule the visit as soon as possible. eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (see Appendix B). At the Screening Visit only, the hematology panel will include HbA1c and APOE E4 genotyping. At the Screening Visit only, the chemistry panel will include TSH, T3, T4, folic acid, and vitamin B12.

Urine will be obtained as indicated in Appendix A and sent to a central laboratory for complete urinalysis. See Appendix B for a complete list of analytes.

An FSH test and urine pregnancy test will be performed at the Screening Visit prior to participation in the study for women <55 years of age for whom it has been ≥1 year since their last menstrual period. Urine pregnancy test will be repeated at EOT/ET Visit (V6).

Vital Signs

Vital signs will be taken as indicated in Appendix A. Vital signs will include body temperature, heart rate, and triplicate blood pressure (systolic and diastolic) measurements.

Height and weight will be measured at the Screening Visit and will be used to calculate body mass index. Weight only will be measured at the EOT visit as indicated in Appendix A. Measurement of weight should be performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.

Electrocardiograms

A single, standard 12-lead ECG will be performed by the Investigator or trained site personnel at the Screening Visit. and at the EOT visit

Physical and Neurological Examinations

Physical and neurological examinations will be performed as indicated in Appendix A.

Magnetic Resonance Scan

Magnetic resonance imaging of the brain will be performed at Screening and as clinically indicated (only in patients without historical MRI available within 6 months of the Screening Visit). This technology will be used to check for evidence of clinically relevant inclusion/exclusion and safety findings.

The MRI scans will be reviewed by the investigator or qualified designee for immediate patient management. Any clinically significant findings noted at Screening that result in a diagnosis should be recorded as a preexisting condition or AE.

9 STATISTICS

A statistical analysis plan (SAP) will be written. The SAP will provide full details of the analyses and data displays. In case of discrepancies in statistical analyses described in the protocol versus the SAP, the SAP will prevail.

Analysis Populations

The Intent-to-Treat (ITT) Population will include all patients who receive at least 1 dose of study drug.

The Per-Protocol (PP) Population will include all patients who have a study drug compliance percentage of at least 80% over the entire study duration. The PP Population will be the primary population used for the PD and PK analyses, and for the analyses of the effects of obicetrapib on cognition.

The Safety Population will include all patients who receive at least 1 dose of study drug. The Safety Population will be the primary population used for the safety analyses.

Statistical Methods

All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include number of patients (n), mean, standard deviation (SD), median, minimum, and maximum values. Analysis of categorical variables will include frequency and percentage.

No formal hypothesis will be tested in this study.

9.1.1 Analysis of Pharmacodynamics, Effects on Cognition, Pharmacokinetics

The PP Population will be the primary population for the PD and PK analyses, and for the analyses of the effects of obicetrapib on cognition. The PD, PK, and effects of obicetrapib on cognition will also be analyzed using the ITT Population as supportive analysis.

9.1.1.1 Primary Pharmacodynamics Analysis

The primary PD endpoint will be summarized descriptively. No statistical interference will be applied to the primary PD endpoint.

9.1.1.2 Exploratory Analyses

All exploratory endpoints (further PD, effects on cognition, and PK) will be summarized descriptively. No statistical inference will be applied to the exploratory endpoints.

9.1.2 Analysis of Safety

The Safety Population will be the primary population for the safety analyses. All safety endpoints will be summarized descriptively. No statistical inference will be applied to the safety endpoints.

AEs will be categorized by primary system organ class and preferred term as coded using the Medical Dictionary for Regulatory Activities (MedDRA) category designations. Summaries of AEs, including the number and percentage of patients who experience an AE, will be provided.

Laboratory values will be summarized descriptively, including the change from baseline. In addition, shift tables will be presented to describe the change in laboratory parameter values at post-baseline visits using normal range categories (low, normal, and high).

Vital signs will be summarized descriptively, including the change from baseline.

ECG results, as well as physical and neurological examination findings will be listed. Clinically relevant abnormal findings at baseline or during the study will be reported as baseline condition or AE, respectively.

9.1.3 Interim Analysis

No interim analysis is planned for this study.

9.1.4 Sample Size Determination

No formal sample size determination was performed. A total number of 10 to 15 patients is considered sufficient for this proof-of-concept study.

10 DATA MANAGEMENT AND RECORD KEEPING

Data Management

10.1.1 Data Handling

All handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. If an external organization will process data on behalf of the sponsor, a contractual procedure will be signed between the sponsor and the external organization to ensure compliance with the above-mentioned legislation.

Data will be recorded at the site on eCRFs and reviewed by the monitor during monitoring visits. The monitors will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Sample Handling

The actual dates and times of sample collection must be recorded in the eCRF and laboratory requisition form. Samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Refer to the Appendix A for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

Samples will be shipped to analytical laboratories both within and outside of the European Union using unique identifiers that cannot be traced to personal identifiers by the external parties.

10.1.3 Long-term storage of samples

Left-over samples collected in this study may be stored for up to 25 years after the end of the study in the [redacted]
Left-over samples will only be used to understand obicetrapib, to understand AD, to understand differential intervention responders, and to develop tests/assays related to obicetrapib and AD. The research may begin at any time during the study or the post-study storage period. Stored left-over samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers.
Computer Systems Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.4 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must login to the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

10.1.5 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA (latest available version) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.6 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.1.7 Data Protection

The collection and processing of personal data from participants enrolled in this study and study partners will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants and study partners confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, and regulatory inspection. This consent also addresses the transfer of the coded data to other entities and to other countries outside of the European Union. For any exchange of coded data to other entities within the European Union, the privacy of the participant will be protected to an equal level and standard as that of the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. For exchange of coded data to entities in the United States of America, the protection of personal data is not at an equivalent level to the European Union.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records

and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last patient in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

Independent Ethics Committee

It is the responsibility of the Brain Research Centre to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective site(s) once the respective committee's written approval has been given.

Patient recruitment

Patients may be referred to the Brain Research Center via the company's website or directly by their treating physicians. Clinical Research Coordinators at Brain Research Center discuss a variety of clinical trials with interested patients, and aside from inclusion and exclusion criteria, it is entirely the patient's decision if and in which clinical trial they wish to participate. Based on the patient's interest, an initial meeting with a physician at Brain Research Center is scheduled, where the potential participant is introduced to the center and may ask any general questions he/she may have regarding participation in a clinical trial. After this initial conversation, a separate visit is scheduled to discuss a particular trial (again with a physician), when the patient receives the information sheet and can discuss and ask questions about the study. The patient is given as much time as he/she may need to consider participation and may ask further questions to the physician at any point, but a minimum consideration time of 1 week is given before Informed Consent can be signed.

Informed Consent

The term "informed consent" includes all consent and assent given by the patient and by study partners. The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the Independent Ethics Committee (IEC) prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

A study partner must be someone with regular contact with the participant, such as a partner, son/daughter, or a close friend. The study partner must be willing and able to sign an ICF, to accompany the subject to study visits, and adhere to study requirements.

The Investigator must ensure that each study patient and his/her study partner are fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. Participants must be informed that their participation is voluntary. The data privacy rights of all patients will be maintained in accordance with European Union levels. After the initial recruitment period and consideration time (minimum 1 week), the Investigator will obtain written informed consent from

each patient and study partner before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IEC, and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

Reimbursement

Patients will receive reimbursement of travel and parking costs for attendance to the research center during study visits. Further, meals will be provided during visits that may take place around lunch time.

Patient Card

On enrollment in the study, the patient will receive a patient card to be carried at all times. The patient card will state that the patient is taking part in a clinical research study, type of treatment, number of treatment packs received, and contact details in case of an SAE.

Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the monitor will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

Disclosure of Data

Data generated by this study must be available for inspection by the Sponsor or their designee, applicable health authorities, and the IEC as appropriate. Patients or their legally authorized representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Publication will be in accordance with the basic principles of Central Committee on Research Involving Human Subjects (CCMO) statement on publication policy.

Insurance and Indemnity

The sponsor has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Legal Aspects

The clinical study is submitted to the relevant national competent authority to achieve a clinical trial authorisation (CTA).

The study will commence (ie, initiation of study site[s]) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by the Brain Research Center Amsterdam or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IEC within 5 working days.

Annual progress report

The Sponsor/designee or Investigator will submit a summary of the progress of the trial to the accredited IEC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

Temporary half and (prematurely) end of study report

The Sponsor/designee or Investigator will notify the accredited IEC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The Sponsor/designee or Investigator will notify the IEC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the Sponsor/designee or Investigator will notify the accredited IEC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the Sponsor/designee or Investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited IEC and the Competent Authority.

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APPENDIX A: SCHEDULE OF PROCEDURES

Study period	**Screening**	**Treatment Period**					**Follow-Up ■ (V7)**
		Baseline (V2)	**V3**	**V4**	**V5**	**EOT/ET[9] (V6)**	
Day (±Visit Window)	**1-8 weeks**	**D1**	**D42 ±6d**	**D84 ±6d**	**D126 ±6d**	**D168 ±6d**	**D198 ±6d**
Informed consent[1]	X						
Inclusion/exclusion criteria	X	X					
Demographic data	X						
Medical history and baseline conditions	X						
C-SSRS		X	X	X	X	X	
Height and weight[2]	X					X	
Vital signs[3]	X	X	X	X	X	X	
ECG[4]	X					X	
FSH test[5]	X						
Urine pregnancy test[5]	X					X	
Hematology, chemistry and urinalysis	X	X[6]	X[7]	X[6]	X[7]	X	
HbA1c	X						
Thyroid function	X						
Folic acid and vitamin B12 levels	X						
APOE E4 testing	X						
MRI-cerebrum[11]	X						
Physical examination	X	X		X		X	
Neurological examination	X	X		X		X	
Prior and concomitant medications	X	X	X	X	X	X	
Dispense study drug		X	X	X	X		
Study drug administration[8]		X	X	X	X	X	
Study drug compliance check			X	X	X	X	
Adverse events	X	X	X	X	X	X	X
CDR	X						
MMSE	X	X		X		X	
CFC		X				X	
Plasma sample for PD and PK		X		X[12]		X[12]	
CSF sample for PD and PK	X			X[10]		X	

APOE E4 = apolipoprotein E-E4; CFC = Cognitive-Functional Composite; CDR = Clinical Dementia Rating; ECG = electrocardiogram; EOT = End of Treatment; ET = Early Termination; HbA1c = hemoglobin A1c; MMSE = mini-mental state examination; MRI = magnetic resonance imaging.

Note: In cases of COVID-19 limitations, it is the Investigator's responsibility to assure the safety of patients, including phone or video contact to assess the patient's well-being including any adverse event, collection of study samples and clinical data as best as possible, and direct shipment of study drug to the patient, if necessary. Where available and appropriate, home health care may be considered to facilitate monitoring of safety and study continuity. Documentation of these cases and the study site's management of patients should be recorded in the Investigator study files. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

1. Signed informed consent must be obtained before any study-related procedures are performed.
2. Height and weight will be measured at the Screening Visit and will be used to calculate body mass index. Weight only will be measured at the EOT visit. Measurement of weight should be performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.
3. Vital signs will include body temperature, heart rate, and triplicate blood pressure (systolic and diastolic) measurements.
4. A single, standard 12-lead ECG will be performed by the Investigator or trained site personnel at the Screening Visit and at the EOT visit.
5. FSH test and urine pregnancy test will be performed in women <55 years of age
6. Only clinical chemistry panel to be performed (Appendix B)
7. Clinical chemistry and part of hematology (PT, PTT, INR and platelets) only (Appendix B)
8. Study drug will be administered by the patient orally and once daily on Days 1 through 168. Study drug should be administered at approximately the same time each morning.
9. Early Termination Visit only for patients who withdraw prematurely from the study.
10. Optional lumbar punction.
11. MRI is to be performed only in patients without historical MRI available within 6 months of the Screening Visit.
12. A single trough PK sample will be drawn on Day 84 and 168 *prior to dose* to measure trough levels of obicetrapib

APPENDIX B: CLINICAL LABORATORY ANALYTES

Chemistry Panel

Alanine aminotransferase (ALT)	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase (AST)	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase (CK)
Creatinine	Estimated glomerular filtration rate (eGFR) [1]
Folic acid [2]	Gamma-glutamyl transferase
Glucose (fasting)	C-reactive protein
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Thyroid stimulation hormone (TSH) [2]
Thyroxine (T4) [2]	Total bilirubin
Total protein	Triiodothyronine (T3) [2]
Uric acid	Vitamin B12 [2]

[1] Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation: https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr.
[2] Screening Visit only.

Endocrinology

Follicle-stimulating hormone – At screening visit only for women <55 years of age

Hematology

Hemoglobin A1c (HbA1c) [1]	Hematocrit
Hemoglobin	International normalized ratio (INR)
Partial thromboplastin time (PTT)	Platelets
Prothrombin time (PT)	Red blood cell count
White blood cell count and differential [2]	APOE E4 genotyping [1]

[1] Screening Visit only.
[2] Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

[1] Microscopy is performed only as needed based on positive dipstick test results

Pregnancy Test

Urine – At screening and V6 for women <55 years of age

Pharmacodynamic parameters

CSF:

- ApoA-I, ApoE, small HDL particles and ABCA1-driven cholesterol efflux, HDL-C, HDL-ApoE, ApoA-II
- YKL40
- sTREM2
- 24-hydroxycholesterol and 27-hydroxycholesterol
- Tau and p-Tau 181, $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio, neurogranin, neurofilament light, GFAP
- Inflammatory markers (eg, IFN-γ, IL-10, IL-12p70, IL-17A, IL-6, TNF-α)

Plasma:

- TC, ApoA-I, ApoE, ApoB, LDL-C [1], Non-HDL-C, TG, small HDL particles and HDL-C, HDL-ApoE, ApoA-II
- 24-hydroxycholesterol and 27-hydroxycholesterol
- Tau and p-Tau epitopes, $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio, neurofilament light

[1] Measured by preparative ultracentrifugation, also referred to as beta quantification.

APPENDIX C: SUMMARY OF CHANGES ORIGINAL PROTOCOL TO V2.0

Rationale/Background for Changes

The changes in Version 2.0 (dated 09 September 2021) reflect adaptations requested by the Ethical Committee and/or the U.S. Food and Drug Administration agency. These changes were incorporated during the review of the study protocol and therefore do not constitute a protocol amendment.

Major changes since Version 1.0 include the following:

- Addition of an exclusion criteria related to pharmacologic agents known to significantly induce or inhibit drug-metabolizing enzymes
- Clarification of participants' decision when undergoing assessments for an Early Termination Visit
- Removed references to participant's legal representative
- Introduced the option to review a historical MRI (<6 months from Screening) for eligibility assessment
- Included a scale to assess suicidality during the study (Columbia Suicide Severity Scale)
- Included assessments of PT, PTT, INR and platelets during Visits 3 and 5 to assess risk for complications/bleeding during lumbar punctures at subsequent Visits
- Adjusted process of SAE reporting to reflect study agreement to use a paper report form
- Clarified that data handling will occur following EU General Data Protection Regulation and Dutch Act on Implementation of the General Data Protection Regulation
- Included sections on Sample Handling and Long-term storage of samples
- Included section on Data Protection
- Included section on Patient Recruitment to describe the patient's journey
- Introduced a minimum of 1-week consideration period prior to signature of informed consent
- Included a section on Reimbursement
- Adjusted the Publication Policy and Insurance and Indemnity sections to conform with requirements from the Dutch Regulatory Authorities
- Included sections on Progress Report and Temporary Halt/End of Study Report to the ethical committee
- Clarified that on Day 84 and 168 a singe trough PK sample will be drawn prior to dose

Summary of Changes

Description Update to the exclusion criteria. Exclusion criteria #8 was revised to include any pharmacologic agent known to significantly induce or inhibit drug-metabolizing enzymes (especially inducers and inhibitors of CYP3A4 and CYP2C9) as part of the list of prohibited medications within 30 days of initial dosing

Rationale

As obicetrapib is mainly metabolized by CYP3A4 and CYP2C9, it is important to exclude patients treated with strong CYP3A4 and CYP2C9 inducers and inhibitors from the clinical protocol.

Protocol Sections Affected

4.2 Exclusion Criteria

Description Clarification of participant's decision when undergoing assessments for an Early Termination Visit

Rationale

In the previous protocol version, it was stated that study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination Visit. This remains relevant as documenting participants' complete status when assessing early termination may provide valuable information regarding safety and tolerability. However, the ethical committee requested that it is made explicit in the protocol that the patient always has the final decision and is not obligated to complete the assessments if he/she does not wish to.

Protocol Sections Affected

4.5 Withdrawal Criteria

Description Removed any mention of the participants' legal representative from all sections of the protocol

Rationale

In the previous protocol version, it was assumed that if patients would lose the capacity to consent during the study, a legal representative may act on his/her behalf when deciding to continue participation in the study. During the ethical committee review, the probability of the situation arising was raised, since the study includes patients with early Alzheimer's disease. Therefore, it was determined that the probability of such a situation was too low to warrant the need for a legal representative, and decided that only participants who retain their capacity to consent will remain in the study.

Protocol Sections Affected

6.1 Screening Visit

11.4 Informed Consent

Description Introduced the option to utilize a historical MRI for the purposes of eligibility screening. This MRI must not be older than 6 months from the Screening Visit.

Rationale

In order to avoid unnecessary study procedures and considering many (if not all) potential participants will have undergone an MRI session recently due to the standard of care for patients with Alzheimer's disease, it was decided that a recent historical MRI can be used by the physician to determine eligibility.

Protocol Sections Affected

6.1 Screening Visit

8.11 Magnetic Resonance Scan

Appendix A: Schedule of Procedures (footnotes)

Description Addition of the use of the Columbia Suicide Severity Scale throughout the study (from V2, baseline, to V6, end of treatment)

Rationale

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. Because of these concerns, a prospective assessment for suicidal ideation and behavior is recommended to be included in clinical trials involving all drugs and biological products for neurological indications. The FDA recommends that these assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers.

Protocol Sections Affected

6.2 Treatment Period – Visits 2 Through 5

Description Inclusion of assessments of PT, PTT, INR and platelets during Visits 3 and 5

Rationale

Following FDA recommendation, it was decided that including laboratory testing to exclude a predisposition to excessive bleeding should be performed shortly prior to each lumbar puncture. In order to not overburden patients with multiple visits to accommodate this test prior to the lumbar puncture visits, it was decided to perform those in pre-existing study visits directly prior to those with scheduled lumbar puncture. These visits already included blood and plasma sampling and therefore could accommodate this request efficiently.

Protocol Sections Affected

6.2.2 Visit 3

6.2.4 Visit 5

Appendix A: Schedule of Procedures (footnote)

Appendix B: Hematology

Description Adjusted process of SAE reporting to reflect study agreement to use a paper report form

Rationale

Previous wording expected SAE reporting to occur within [redacted] EDC system. However, the current study will be making use of an independent EDC system. As a consequence, the language

around SAE reporting was adapted to reflect the use of paper forms as per [redacted] procedures with external EDC systems.

Protocol Sections Affected

8.3 Serious Adverse Event Reporting – Procedures for Investigators

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Description Clarified that data handling will occur following EU General Data Protection Regulation and Dutch Act on Implementation of the General Data Protection Regulation

Rationale

Following ethical committee review, it was requested that an explicit reference to the applicable regulation was included in the protocol. It has been clarified that all handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. Language was also included to clarify that if an external organization will process data on behalf of the sponsor, a contractual procedure will be signed between the sponsor and the external organization to ensure compliance with the above-mentioned legislation.

Protocol Sections Affected

10.1.1 Data Handling

Description Included sections on Sample Handling and Long-term storage of samples

Rationale

During ethical committee review, the topic of sample handling and storage was raised as some unclarities remained in the protocol. In particular, it has been clarified that samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. It was also made explicit that samples will be shipped and analyzed within and outside of the European Union. Further, the long-term storage of left-over samples was clarified and the biobank used has been mentioned in the protocol. Specification of what these biobank samples can be used for in the future was also included.

Protocol Sections Affected

10.1.2 Sample Handling

10.1.3 Long-term storage of samples

Description Included section on Data Protection

Rationale

During ethical committee review, the topic of data protection was raised especially considering the potential sharing of data outside of the European Union. An addition section was drafted to clarify the procedures undertaken to ensure data protection at all times, from informed consent to analysis of data.

Protocol Sections Affected

10.1.8 Data Protection

Description Included section on Patient Recruitment to describe the patient's journey and introduced a minimum of 1-week consideration period prior to signature of informed consent

Rationale

The ethical committee reviewing the study noted that the patient journey was not clear, in particular with respect to which study staff was responsible for the initial conversation about the study and how long the patient would have to consider participation. A specific section was drafted to describe the patient's journey and make explicit that a minimum 1-week consideration period is applicable.

Protocol Sections Affected

11.3 Patient recruitment

Description Adjusted the Publication Policy and Insurance and Indemnity sections to conform with requirements from the Dutch Regulatory Authorities

Rationale

Standard passages regarding Publication Policy and Insurance and Indemnity are applicable in the Netherlands, and these were not included previously. The appropriate sections were therefore adjusted to align with language from the template provided by the regulatory authorities.

Protocol Sections Affected

11.10 Publication Policy

11.11 Insurance and Indemnity

Description Included sections on Progress Report and Temporary Halt/End of Study Report to the ethical committee

Rationale

Standard passages regarding Study Progress and notification of Temporary Half/End of Study are applicable in the Netherlands, and these were not included previously. The appropriate sections were therefore included following language from the template provided by the regulatory authorities.

Protocol Sections Affected

12.2 Annual progress report

12.3 Temporary halt and (premature) end of study report

Description Clarified that on Day 84 and 168 a single trough PK sample will be drawn prior to dose

Rationale

FDA requested that the exact timepoints at which plasma samples for PK/PD on days 84 and 168 will be drawn are listed to appropriately characterize the PK of obicetrapib at steady state. Since these samples are intended to provide trough drug levels only, a clarification was added to the protocol to state that a single PK sample will be drawn on Day 84 and Day 168 prior to dose to measure trough levels of obicetrapib.

Protocol Sections Affected

Appendix A: Schedule of Procedures (footnote)

APPENDIX D: SUMMARY OF CHANGES IN PROTOCOL V2.0 TO V3.0

Rationale/Background for Changes

The changes in Version 3.0 (dated 29 October 2021) reflect adaptations requested by the Ethical Committee and those to clarify any identified inconsistencies within different protocol sections. These changes were incorporated during the review of the study protocol and therefore do not constitute a protocol amendment.

Major changes since Version 2.0 include the following:

- Confirmation that the level of privacy protection to be maintained for coded data transferred within and outside of the European Union must be equivalent to those applicable by the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation.
- Specification of what constitutes a study partner, in line with the informed consent form (someone with regular contact with the participant such as a partner, son/daughter, close friend, etc)
- Smaller changes to align Appendix B with study visit sections in the protocol with respect to the clinical laboratory analytes to be samples/analyzed per visit
- Removal of the reference to a biobank, which will not be established for this study. The samples will only be kept for (eventual) future use in the context of this study.

Summary of Changes

Description Update to clarify the level of privacy to be maintained within and outside of the European Union. The appropriate section now clarifies that also for coded data transferred, the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation will be followed.

Rationale

During ethical committee review, it was identified that this section was not explicit with respect to the coded data transferred. This has been adjusted accordingly.

Protocol Sections Affected

10.1.7 Data Protection

Description Specification of what constitutes a study partner.

Rationale

The protocol did not specify what is meant with the term “study partner” in previous versions, while the informed consent form did. Following ethical committee request, the appropriate section was adjusted to describe what a study partner is.

Protocol Sections Affected

11.4 Informed Consent

Description Removal of a reference to a biobank, as no biobank will be established with the samples collected in this study.

Rationale

The protocol previously mentioned that besides the 25 year storage of the samples, a biobank would be established within this study. This was an incorrect statement, as the intent is *not* to set-up a biobank, but only to maintain the samples for any eventual use by the Sponsor in the context of this study and the development of the study drug.

Protocol Sections Affected

10.1.3 Long-term Storage of Samples

Description Alignment of study visit sections and Appendix B with respect to the clinical laboratory analytes to be assessed in the study.

Rationale

During protocol review, some changes were not consistently reflected between Appendix B and the individual study visit sections in the protocol. All inconsistencies have been identified and corrected, so that all sections of the protocol reflect the same information with respect to which analytes will be assessed at each visit.

Protocol Sections Affected

6 Study Procedures

Appendix B Clinical Laboratory Analytes

APPENDIX E: SUMMARY OF CHANGES IN PROTOCOL V3.0 TO V4.0

Rationale/Background for Changes

The changes in Version 4.0 (dated 30 November 2021) reflect adaptations requested by the Ethical Committee. These changes were incorporated during the review of the study protocol and therefore do not constitute a protocol amendment.

Major changes since Version 3.0 include the following:

- Clarification that for data transferred to the United States of America, the same level of privacy protection as within the European Union cannot be guaranteed.
- Specification of where the long-term storage of samples is located.

Summary of Changes

Description Update to clarify the level of privacy that cannot be maintained at the level of the European Union for data transferred to the United States of America.

Rationale

During ethical committee review, it was identified that this section was not correct. This has been adjusted accordingly.

Protocol Sections Affected

10.1.7 Data Protection

Description Specification of where long-term storage of samples is located.

Rationale

The protocol did not specify where samples are kept after the end of the study, for long-term storage. This is the [redacted]

Protocol Sections Affected

10.1.3 Long-term storage of samples
