TANGO

Protocol n° CER-001-CLIN-009

PHASE III, MULTI-CENTER, RANDOMIZED, 48 WEEKS, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY TO EVALUATE EFFICACY AND SAFETY OF CER-001 ON VESSEL WALL AREA IN PATIENTS WITH GENETICALLY DEFINED FAMILIAL PRIMARY HYPOALPHALIPOPROTEINEMIA AND RECEIVING BACKGROUND OPTIMIZED LIPID THERAPY, WITH OPTIONAL OPEN-LABEL SAFETY EXTENSION

CLINICAL PHASE : III

EudraCT number : 2015-003713-23

PROTOCOL NUMBER: CER-001-CLIN-009

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Revision History:
Version 1.0 of 4th September 2015
Version 1.1 of 19th October 2015
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Sponsor:

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SYNOPSIS

TITLE OF STUDY:

This is a Phase III, multi-center, randomized, 48 weeks, double-blind, parallel-group, placebo-controlled study to evaluate efficacy and safety of CER-001 on vessel wall area in patients with genetically defined familial primary hypoalphalipoproteinemia and receiving background optimized lipid therapy, with optional open-label safety extension

INVESTIGATIVE SITES:

Approximately 15 sites from Europe, Canada, United States of America, Brazil and Israel to be determined based on availability of patients with this rare disease.

ANTICIPATED STUDY DURATION:

Anticipated Start Date for Study Enrollment: November 2015
Anticipated Completion Date for Study Enrollment: First quarter 2017
Anticipated Date for Last Patient Last Visit: First quarter 2018

OBJECTIVES:

Primary objectives:

- To evaluate the effect of 24-week treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA) as compared to placebo using 3T magnetic resonance imaging (3T-MRI);
- To evaluate the safety and tolerability of CER-001 administered for 24 weeks

Secondary objectives:

- To evaluate the effect of 8-week and 48-week treatment with CER-001 on MVWA as compared to placebo using 3T-MRI;
- To evaluate the effect of 8-week, 24-week and 48-week treatment with CER-001 on femoral artery as compared to placebo using 3T-MRI;
- To evaluate the effect of 24-week treatment with CER-001 in the target (plaque) to background (blood) ratio (TBR) from an index vessel (either right carotid or left carotid) based on the standardized ^{18}FDG uptake measured with PET/CT;
- To evaluate safety and tolerability of CER-001 administered for 48 weeks

Exploratory objectives:

- To evaluate the effect of treatment with CER-001 with respect to other efficacy measurements including carotid artery and carotid normalized wall index using 3T-MRI;
- To evaluate the effect of treatment with CER-001 with respect to potential surrogate markers on vessel wall biology including laboratory variables;
- To evaluate the effect of treatment with CER-001 with respect to inflammation;
- To evaluate plasma-mediated cellular cholesterol efflux capacity;
- To measure ApoA-1 levels (pharmacokinetic parameters);
- To measure cholesterol, triglycerides, lipids and lipoproteins levels.

Other objectives:

- To evaluate safety and tolerability of 72 week treatment with CER-001.
- To evaluate the effect of 72 week treatment with CER-001 on MVWA using 3T-MRI;
- To evaluate the effect of 72 week treatment with CER-001 on femoral artery using 3T-MRI;

BIOMARKER EVALUATION:

Specimens for protein biomarker discovery and validation will be collected from all patients. These specimens could be used for research purposes to identify and/or verify biomarkers that are linked to CER-001 treatment and could help to understand the pathogenesis, course and outcome of the disease of the targeted patient population.

METHODOLOGY:

Patients with genetically defined familial primary hypoalphalipoproteinemia (FPHA – mutation in ApoA1 and/or ABCA1 gene), receiving background optimized lipid therapy AND with cardiovascular disease background will be enrolled in the study.

Enrolled patient will receive 29 infusions of CER-001 or placebo over 48 weeks.

After obtaining written informed consent and if the patient is eligible, he/she will receive twenty nine 8 mg/kg doses of CER-001 or placebo, administered as a weekly infusion during the first 8 weeks (9 doses) and then every two weeks during the following 40 weeks (20 doses).

Patients will have a safety follow-up visit 4 weeks after the last dose administration.

NUMBER OF PATIENTS:

A total of 30 patients will be randomized.

PRODUCT INFORMATION

TREATMENT GROUPS:

CER-001 is a negatively charged ApoA-1-containing lipoprotein/phospholipid complex mimicking natural HDL.

COMPARATOR PRODUCT:

Standard sodium chloride solution will be used as the placebo.

ASSESSMENTS:

- Vascular structural changes (atherosclerotic plaque burden assessed by 3T-MRI)
- Vascular inflammation as measured by ^{18}FDG-PET/CT

- Safety parameters (physical examination, vital signs, clinical laboratory measurements, electrocardiograms (ECGs), metabolic parameters, adverse events (AEs), urine analyses and anti-ApoA-1 antibody development)
- Pharmacokinetic (PK) parameters (assessed by ApoA-1 levels, cholesterol mobilization)
- Pharmacodynamic parameters (lipids, lipoproteins and apolipoproteins)

SAMPLE SIZE CALCULATION:

The assumptions, upon which the power calculation are based, are data from the 7 patients completing the CER-001-CLIN-007 SAMBA study, given the similarity of the genetic mutations. Those patients presented with a median value for MVWA of 25.0 mm^2 and had a follow-up median value at 6 months of 21.8 mm^2. The mean percent reduction is reported as 6.7%, standard deviation = 4.5%. These observed values would provide a conservative estimate of the effect of CER-001 in the more severe population for this FPHA study.

Using these results from SAMBA (i.e. an assumed standard deviation of 4.5%) and a 2:1 randomization scheme to maximize exposure to active drug, 16 completing patients in the CER-001 group and 8 in the placebo group (24 total completers for mITT) would yield 90% power to detect a difference from baseline versus placebo of 6.7%, using two-tailed testing with α=0.05. A total of 30 patients are planned to be randomized that would provide a buffer such that a 20% discontinuation rate would still allow the study to retain sufficient power for a supporting per protocol efficacy analysis (MVWA).

PRIMARY EFFICACY PARAMETER:

The primary efficacy parameter of this study will be the change from baseline after 24 weeks treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA) as compared to placebo using 3T-MRI when administered to patients with genetically defined FPHA.

SECONDARY EFFICACY PARAMETERS:

- Change from baseline after 8-week and 48-week treatment with CER-001 on MVWA as compared to placebo using 3T-MRI when administered to patients with genetically defined FPHA.
- Change from baseline after 8, 24 and 48 weeks treatment with CER-001 on femoral artery as compared to placebo using 3T-MRI when administered to patients with genetically defined FPHA.
- Change from baseline at 24 weeks in the TBR from an index vessel (either right carotid or left carotid) based on the standardized ^{18}FDG uptake measured with PET/CT in patients with genetically defined FPHA.

SECONDARY SAFETY PARAMETERS:

- Incidence and severity of AEs from routine monitoring.
- Incidence of abnormalities and changes from baseline in clinical laboratory parameters from testing of blood and urine, including anti-ApoA-1 antibody.

Incidence of cardiovascular events.

EXPLORATORY EFFICACY PARAMETERS:

- Changes from Baseline in carotid normalized wall index assessed by 3T-MRI from baseline to week 24 and week 48.
- Changes from baseline to week 24 and week 48 of potential markers on vessel wall biology including and not restricted to laboratory variables such as absolute and relative change in high sensitivity C-reactive protein (hs-CRP), MMP-9 and other selected inflammatory markers (TNFα, IL-6), soluble VCAM-1, PON-1 and sMCP1, plaque characterization indexes using 3T-MRI.
- Cholesterol efflux capacity after CER-001 administration.
- Changes from baseline of ApoA-1 level.
- Changes from baseline in total cholesterol, unesterified cholesterol, esterified cholesterol, triglycerides, apolipoprotein B, other apolipoprotein and lipoprotein profiles for total and unesterified cholesterol by HPLC.

OTHER EFFICACY PARAMETERS:

- Change from baseline after 72 week treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA) using 3T-MRI when administered to patients with genetically defined FPHA
- Change from baseline after 72 week treatment with CER-001 on femoral artery using 3T-MRI when administered to patients with genetically defined FPHA

SELECTION OF STUDY PATIENTS

Patients with ApoA-1 ≤ 110mg/dL and HDL≤ 35 mg/dL ,with suspected homozygous or heterozygous mutation in the *ABCA1,* and/or *ApoA-1* genes confirmed by genetic testing, and background of symptomatic or asymptomatic cardiovascular disease, will be eligible for this study..

Patients who fulfill all inclusion/exclusion criteria, including confirmation of a genetic defect, may be enrolled in the study.

INCLUSION CRITERIA

Eligible patients must meet the following criteria before they are enrolled in the study:

1. Male and female patients, aged 18 and above.
2. Female patients who are not either surgically sterile (e.g., tubal ligation or removal of ovaries or uterus) or post-menopausal (no spontaneous menstrual periods for at least one year) must agree to use one of the following forms of contraception from screening until 90 days after the completion of the study medication: (1) systemic hormonal treatment (2) an IUD which was implanted at least 2 months prior to screening or (3) "double-barrier" contraception (condom, diaphragm and spermicide are each considered a barrier), or (4) agree to remain sexually abstinent during the entire study period (when contraception is not acceptable for cultural or religious beliefs)

3. Sign written informed consent after the scope and nature of the investigation have been explained to them before screening evaluations and willing to comply with the study restrictions
4. Are fluent in the language of the investigator, study staff (including raters), and the informed consent
5. Diagnosis of genetically confirmed HDL-c deficiency due to defects in genes coding for e.g. ABCA1 and/or ApoA-1
6. IF the subject is on lipid-lowering therapy or NEEDS to be treated with lipid-lowering therapy then the subject must be on a stable dose at least 6 weeks prior to the baseline procedures.
7. Background symptomatic or asymptomatic cardiovascular disease should be present as such:

- For symptomatic cardiovascular disease: i) history of cardio or cerebrovascular events, ii) diagnosed coronary artery disease (CAD), iii) diagnosed carotid or peripheral stenosis, iv) previous myocardial revascularisation - percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG).
- For asymptomatic cardiovascular disease: patients with subclinical atherosclerosis diagnosed using imaging method such as i)vDoppler ultrasound, ii)vB-mode ultrasonography – measurement of carotid intima media thickness, iii)vintravascular ultrasonography, iv) Computed Tomography, v) Magnetic Resonance Imaging

8. ApoA-1 $\leq$ 110 mg/dL
9. HDL-cholesterol $\leq$ 35 mg/dL or 0.9 mmol/L

EXCLUSION CRITERIA

Patients meeting any one of the following criteria are not eligible for the study:

1. Patient with LCAT mutation will be excluded
2. Patient who experienced a cardiovascular event within 6 months prior to the start of screening
3. Patient who experienced stroke or other cerebrovascular event within 1 year prior to the onset of screening
4. Patients with triglycerides level above 500 mg/dL
5. The patient has evidence of clinically significant, uncontrolled or unstable cardiovascular, renal, hepatic (incl. AST or ALT at or above 3x ULN, or bilirubin at or above 2x ULN), gastrointestinal, hematologic, immunological, neurological, endocrine, metabolic or pulmonary disease (as determined by medical history, clinical laboratory or ECG results, or physical examination) or any other medical disorder that would increase the risk associated with taking study medication or would confound the interpretation of study results.
6. Patients with a body mass index (BMI) < 17 kg/m^2 or > 40 kg/m^2
7. Patients with severe anemia defined as hemoglobin level below or equal to 10 g/dL

8. Any clinically significant abnormal laboratory data, vital signs, physical examination at screening or baseline, which in the opinion of the investigator, would interfere with safety assessments
9. Clinically significant ECG abnormality at screening, including sinus bradycardia (resting heart rate < 50 beats per minute), 2nd or 3rd degree atrioventricular block, prolonged QTc (QTcF ≥ 450 ms in males and ≥ 470 ms in females) history of congenital long QT syndromes, or risk of Torsades de Pointes because of family history of sudden death, etc.
10. Positive result on the serum pregnancy test or are breast feeding at screening, or intend to become pregnant during the course of the trial
11. Male intending to father a child during the study
12. Likely to be unreliable as a study participant based on the Investigator's (or designee's) knowledge of the patient (e.g., alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis)
13. Symptomatic (NYHA Class II or greater) congestive heart failure requiring and persisting despite appropriate medical treatment
14. Uncontrolled blood pressure: systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg at screening or any other pre-randomization visit
15. Uncontrolled diabetes mellitus defined as HbA1c >10%
16. Unexplained creatine phosphokinase level > 3 times the ULN
17. History of malignancy during the 3 years prior to screening, with the exception of basal cell carcinoma of the skin
18. Current alcohol or drug abuse or history thereof within 5 years prior to screening
19. Contraindication to MRI scanning such as imbedded metal (e.g., schrapnel), implanted metal objects (e.g., pacemaker), claustrophobia
20. Participated in any investigational study or taken an investigational drug within 30 days (or 5 times the half-life of the investigational drug, whatever is longer)
21. Ever received CER-001 within 6 months before the start of screening
22. Medically non-compliant in the management of their disease in the investigator's opinion

SAFETY AND TOLERANCE

- Incidence and severity of AEs from routine monitoring
- Incidence of abnormalities and changes from baseline in clinical laboratory parameters from testing of blood and urine
- Incidence of adverse changes from baseline vital sign values
- Incidence of adverse changes from baseline physical examinations
- Safety parameters will also be summarized by genetic subset to identify possible trends

SAFETY EVALUATION

All patients who have received at least one dose, or any part of one dose, of study drug and have a subsequent safety evaluation will be included in the safety analyses. All adverse events reported during the study will be listed, documenting course, severity, relationship to study drug, and outcome. Adverse events will be coded to MedDRA terms.

Adverse events will be summarized, giving the number of patients who experienced an adverse event, the maximum severity, relationship to study drug and body system. Laboratory parameters, vital signs, and physical exam results will be listed and summarized with the statistics of number of patients, mean, standard deviation, median and range or frequencies and percentages, as appropriate, from baseline to each subsequent visit.

ASSESSMENT OF SAFETY

Periodic safety review will be performed during the on-treatment period by a data and safety monitoring board (DSMB) to include surveillance of laboratory testing and on-treatment safety events so as to advise the study management team regarding potential changes in patients monitoring or treatment plans during the remaining treatment period.

Cerenis Therapeutics

PROTOCOL APPROVED BY SPONSOR'S REPRESENTATIVES:

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I have read this protocol and agree to conduct the study as outlined herein, in accordance with the Good Clinical Practices (cGCPs; ICH E6), the Declaration of Helsinki amended, Fortaleza, Brazil, October 2013, the standard operating procedures, local regulatory requirements and complying with the obligations and requirements of clinical Investigators and all other requirements listed in Code of Federal Regulations, FDA title 21 part 312 (21 CFR part 312).

I agree to comply with procedures and all applicable regulations for data recording and reporting including Serious Adverse Event.

I agree to authorize direct access to source data for monitoring, auditing and inspection.

I agree to retain the trial-related essential documents until the Sponsor informs these documents are no longer needed.

I agree to dispense, track and retain study drug in accordance with GCP & protocol.

I agree to inform all patients in this study completely concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with GCPs and Regulatory Authority requirements.

I will be responsible for maintaining each patient's consent form in the study file and providing each patient with a signed copy of the consent form.

Investigator Signature: _____ Date: _____

PROTOCOL APPROVED BY PRINCIPAL INVESTIGATOR

Site Number _____

Investigator Name: _____

Investigator Address: _____

_____

Telephone: _____

Fax/Email: _____

I have read this protocol and agree to conduct the study as outlined herein, in accordance with the Good Clinical Practices (cGCPs; ICH E6), the Declaration of Helsinki amended, Fortaleza, Brazil, October 2013, the standard operating procedures, local regulatory requirements and complying with the obligations and requirements of clinical Investigators and all other requirements listed in Code of Federal Regulations, FDA title 21 part 312 (21 CFR part 312).

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Investigator Signature: _____ Date: _____

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PART 1: STUDY DESIGN AND CONDUCT

1 STUDY RESPONSIBILITIES

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1 STUDY RESPONSIBILITIES (cont.)

Clinical Trial Material Labelling and Packaging

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2 LIST OF ABBREVIATIONS

ABCA1	ATP Binding Cassette transporter A1
ACS	Acute Coronary Syndrome
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
ApoA-1	Apolipoprotein A-1
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CAD	Coronary Arterial Disease
CE	Cholesterol Ester
CER-001	Experimental compound under study
CHD	Coronary Heart Disease
CHO	Chinese Hamster Ovary
CK	Creatine Kinase
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CVD	Cardiovascular Disease
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ESF	Eligilibity Screening Form
FDA	Food and Drug Administration
^{18}FDG-PET/CT	^{18}F-Fluorodeoxyglucose-Positron Emission Tomography/Computerized Tomography
FH	Familial Hypercholesterolemia
FPHA	Familial Primary Hypoalphalipoproteinemia
HbA1c	glycated Hemoglobin A1C
HDL	High density lipoprotein
HDL/LDL RATIO	High density lipoprotein/low density lipoprotein ratio
HDL-C	High density lipoprotein cholesterol
HEENT	Head, Ears, Eyes, Nose, Throat
HPLC	High-Pressure Liquid Chromatography
HR	Heart Rate
hsCRP	high sensitivity C-reactive protein
ICH	International Conference on Harmonization
IL-6	Interleukin 6
IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent-to-Treat
IUD	IntraUterin Device
IVUS	IntraVascular UltraSound
IWRS	Interactive Web Response System
LCAT	Lecithin Cholesterol AcylTransferase
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol

MACE	Major adverse cardiovascular event
Med-DRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
mITT	modified Intent To Treat
MMP9	Matrix Metallopeptidase 9
MRI	Magnetic Resonance Imaging
MVWA	Mean Vessel Wall Area
NSF	Nephrogenic Systemic Fibrosis
PAV	Percent Atheroma Volume
PCI	Percutaneous Coronary Intervention
PET-CT	Positron Emission Tomography–Computed Tomography
PK	Pharmacokinetic
PL	Phospholipid
PON-1	Serum paraoxonase/arylesterase 1
RBC	Red Blood Cells
RLT	Reverse Lipid Transport
RR	Respiratory Rate
SAE	Serious Adverse Effect
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SGPT (ALT)	Serum glutamic-pyruvic transaminase/Alanine aminotransferase
SGOT (AST)	Serum glutamic-oxaloacetic transaminase/Aspartate amino transferase
sMCP1	Soluble monocyte chemoattractant protein 1
SUSAR	Suspected Unexpected SeriousAadverse Reaction
TAV	Total Atheroma Volume
TBR	Target to Background Ratio
TEAE	Treatment Emergent Adverse Events
TNFα	Tumor Necrosis Factor α
3T-MRI	3T- Magnetic Resonance Imaging
UAP	Unstable Angina Pectoris
UC	Unesterified cholesterol
ULN	Upper Limit of Normal
VCAM-1	Vascular cell adhesion protein 1
WBC	White Blood Cell

3 BACKGROUND

3.1 Background on disease familial primary hypolipoproteinemia (FPHA)

ATP binding cassette transporter A1 (ABCA1) and Apolipoprotein (ApoA-1) deficiencies are underlying causes of familial primary hypoalphalipoproteinemia (FPHA). FPHA is caused by genetic defect in one or more of the genes responsible for high-density lipoprotein (HDL) synthesis/maturation, such as ABCA1 and ApoA-1, and is associated with a very low number of HDL-particles, also reflected in a very low plasma concentration of ApoA-1. The disease is also generally associated with a positive family history of low HDL-cholesterol (HDL-C) or premature cardiovascular disease.

The underlying aetiology for all clinical phenotypes of ABCA1 and ApoA-1 deficiencies is the imbalance in cholesterol metabolism. The major carriers for cholesterol in the blood are lipoproteins, including the low-density lipoprotein (or LDL) particles, and the HDL particles. In a healthy human body, there is a balance between the delivery and removal of cholesterol. The LDL particles deliver cholesterol to organs, where it can be used to produce hormones, maintain healthy cells, and be transformed into natural products that assist in the digestion of lipids. The HDL particles remove cholesterol from arteries and tissues to transport it back to the liver for storage, recycling, and elimination through a pathway called “reverse lipid transport (RLT)”.

Mutations in the key HDL gene products, like ABCA1, ApoA-1 and lecithin:cholesterol acyltransferase (LCAT), result in low circulating levels of HDL particles in these patients and, as such, an absent or deficient RLT capacity which is insufficient to prevent the accumulation of cholesterol in the peripheral tissues and results in the development of premature cardiovascular disease.

Current management of patients with FPHA is very limited and is focused on diet control and aggressive LDL-cholesterol (LDL-C)-directed pharmacotherapy that has proven useful adjuncts for managing overall cardiovascular risk. There is no treatment currently available, which can directly restore normal HDL levels/functioning.

Epidemiological studies have consistently shown that decreased HDL-C levels (hypoalphalipoproteinemia) are strongly associated with an increased risk of developing Coronary Arterial Disease (CAD) (1, 2).

<u>Mutations in ApoA-1</u>

Several mutation variants of ApoA-1 have been identified. Homozygous patients have almost undetectable plasma ApoA-1 and HDL-C levels. Heterozygosity often results in approximately half-normal plasma ApoA-1 and HDL-C concentrations (2). However, there are also many heterozygous

variants that do not seem to affect HDL-C levels. Class I mutations prevent the synthesis of ApoA-1 and are associated with accumulation of cholesterol in tissues, manifesting clinically as xanthomatosis, corneal opacity and premature atherosclerosis in the affected individuals. Class II mutations lead to the production of truncated proteins and are variably associated with coronary risk. Class III mutations cause the synthesis of an ApoA-1 species with a grossly altered conformation that is not able to associate with LCAT, thus causing corneal opacity but not necessarily premature coronary heart disease (CHD).

Approximately 25 patients with complete ApoA-1 deficiency have been reported by different authors (3-5). Almost all cases were characterized by the absence of or low levels of HDL-C, and coronary artery disease (CAD) was present in 11 of these patients; 13 of the remaining cases were below age 50, perhaps before clinical atherosclerosis could become manifest. A family clustering of ApoA-1 deficiency in Brazil caused by intermarriage has been reported (6), where a detailed description of two brothers indicated significant cardiovascular disease by their early 40s. One of these brothers was enrolled as the index patient in the CER-001 Phase II SAMBA study (CER-001 CLIN-007) (7).

Mutations in ATP-binding cassette transporter 1 (ABCA1)

In humans, homozygous mutations in the ABCA1 gene leading to defective or non-functional ABCA1 receptors result in Tangier disease, characterized by profoundly decreased HDL-C, ApoA-1 and ApoA-II levels, reduced total and LDL-C and ApoB, and elevated plasma triglyceride levels. With ABCA1 deficiency, ApoA-1 is rapidly cleared before it is able to acquire cholesterol. The cholesterol storage disorder that occurs with ABCA1 mutations might thus possibly be more a consequence of HDL deficiency than a direct consequence of dysfunctional ABCA1 (8).

Homozygous (Tangier disease) patients develop peripheral neuropathy and premature CHD, caused by cholesteryl ester (CE) deposition in a variety of cell types, although the CHD risk differs from one kindred to another, probably because of the reported genetic heterogeneity of the disease (2). Even in heterozygote ABCA1 deficiency patients, radiolabeled HDL was more rapidly catabolized than in healthy controls. Therefore, the metabolic basis of Tangier disease is a rapid catabolism of ApoA-1 and HDL, rather than a defect in their biosynthesis (9). This condition results in an accumulation of CE in many tissues throughout the body, and fibroblasts are characterized by defective efflux capacity. The deposition of CE in the reticuloendothelial organs results in orange-coloured tonsils.

The overall data emerging from studies evaluating patients with ABCA1 mutations are indicative of a link with the development of atherosclerosis and increased vascular disease risk (10, 11).

3.2 Atherosclerosis in FPHA

Atherosclerosis is thought to develop following an imbalance in which there is too much cholesterol delivery by LDL particles relative to the amount of removal by HDL particles.

In animal studies, increasing HDL-C in transgenic mice and rabbits by overexpressing ApoA-1, a major protein in HDL-C, was associated with protection against diet-induced atherosclerosis (12-14).

In humans, FPHA has been reported as highly correlated with higher incidence of premature CAD (15, 16) and tissue cholesterol efflux was decreased in patients with FPHA which co-incided with accelerated and premature atherosclerosis (17).

3.3 Investigational Product

Cerenis Therapeutics has developed CER-001, a negatively charged lipoprotein complex mimicking natural, nascent discoidal pre-HDL, consisting of a combination of two naturally occurring phospholipids and recombinant human ApoA-1. The ApoA-1 protein component is expressed in mammalian CHO cells and purified by a three-step column chromatography process. This purified protein is also referred to as CT70246. The phospholipid component consists of egg sphingomyelin (Sph), and 1, 2-dihexadecanoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (Dipalmitoylphosphatidyl-glycerol; DPPG) in a 97:3 weight ratio. The ratio of protein to total phospholipids in the CER-001 complex is 1:2.7 weight/weight (w/w). The drug product, CER-001 Sterile Solution for Infusion, is a solution of the CER-001 complexes in phosphate buffered sucrose/mannitol solution (10 mM phosphate buffer, 4.0% sucrose, 2.0% mannitol, pH 8.0). The concentration of CER-001 complexes in the formulation is expressed as the concentration of the ApoA-1 protein component of the complex. CER-001 is intended for the treatment of complications due to atherosclerotic diseases.

3.3.1 Non-Clinical Findings for CER-001

CER-001, a recombinant human ApoA-1/phospholipid complex, was well-tolerated at the dose of 100 mg/kg in rats and monkeys given intravenously (IV), every second day for 4 weeks. A dose of 20 mg/kg, in both species, was considered a dose with no adverse effects in the 4-week dosing studies. CER-001 caused dose-dependent increase in total and free cholesterol, an expected pharmacodynamic effect, as a result of cholesterol mobilization, in both species. CER-001 also caused moderate-to-marked, but transient, increases in liver transaminases, ALT and AST, alkaline phosphatase, total bilirubin and triglycerides at higher doses of 100 mg/kg and above. These changes were generally reversible within 24 to 48 hours post-dose.

Pathological changes in rats included decreased red blood cell indices (evidence of anemia associated with reticulocytosis) consistent with regenerative anemia, dose-related mild-to-moderate hemopoiesis in spleen at 50 mg/kg and above and cholangitis or pericholangitis in liver at 100 mg/kg. These changes were considered secondary to increased cholesterol mobilization and reversible during the treatment-free period.

Liver, spleen and bone marrow were considered target organs of toxicity effect of CER-001. Liver enzyme and renal parameter changes noted in single dose study in rat and rising dose study in monkey at doses 100 mg/kg and above were considered transient and secondary to exaggerated pharmacological effects. These changes were completely reversible within a short treatment-free period.

CER-001 did not cause any treatment-related effects on neurobehavioral parameters and respiratory safety parameters in rats; cardiovascular and respiratory safety parameters evaluated in monkeys implanted with telemetry device at doses up to 100 mg/kg, except but small statistically significant increase in heart rate at 100 mg/kg.

CER-001 did not induce any antibodies against human ApoA-1 in rats after alternate day dosing of CER-001 over a 4 week period. In monkeys, antibodies against human ApoA-1 were detected after alternate day dosing of CER-001 over a 4 week period as well as during the subsequent treatment free period. Further characterization of these antibodies in primates is still being conducted.

3.3.2 Clinical Findings for CER-001

A Phase I single dose tolerance study has been completed in 32 patients. Single doses of 0.25, 0.75, 2.0, 5.0, 10.0, 15.0, 30.0 and 45.0 mg/kg of CER-001 were administered to 32 healthy dyslipidemic volunteers in a randomized, double-blind, placebo-controlled, cross-over, single rising dose safety and tolerance study. CER-001 was well-tolerated in all patients, with an adverse event profile similar to that observed with placebo. CER-001 did not appear to affect clinical chemistry or hematology safety parameters differently than placebo. No adverse effects of CER-001 on ECGs, vital signs, or physical findings were observed. No antibodies against ApoA-1 developed following single doses. All related data can be found in the fifth version of the Investigational Brochure (7).

One Phase II pilot study called EXPRESS, a small 12-patients study in Heterozygous Familial Hypercholesterolemia (FH) to assess MRI and IVUS imaging endpoints, has been completed. The patients enrolled in the study were not representative of the typical high plaque burden/high risk heterozygous FH patient with clinically active atherosclerosis; mean baseline percent atheroma volume (PAV) was only 32% and ranged from 18% to 44%. Non-representative sampling along the length of the coronary arteries by the MHI IVUS Core Lab has raised significant methodological concerns which call into question the appropriateness/applicability of the statistical analysis to the IVUS dataset and the validity of any interpretation of the analytical result relative to the vascular biology of the coronary arteries studied. Given the small number of patients who contributed evaluable data due to measurement difficulties (n=9) and the subsequent methodological concerns, no meaningful conclusions could be drawn regarding the effects of CER-001 on atherosclerotic plaque volume in patients with heterozygous FH. The absence of a detectable treatment response precludes the assessment of the association between the change from baseline in plaque burden measurements as assessed by IVUS and by 3T-MRI. Intravenous infusions of CER-001 administered at a weekly dose of 8 mg/kg for six weeks were well tolerated in these patients with heterozygous FH (*7*).

A second Phase II study called CHI-SQUARE, in patients with Acute Coronary Syndrome has also been completed. It was an ascending dose, placebo-controlled, double-blind, dose-response study that enrolled 507 patients (3:1 ratio active:placebo). The full study report is still in preparation; however, preliminary results indicate that CER-001 did not meet its primary endpoint of a reduction in total atheroma volume (TAV) as measured by IVUS for the 12 mg/kg CER-001 treated patients compared to the placebo patients. Methodological concerns regarding the IVUS analysis, as detected in the EXPRESS study, also pertain to CHI SQUARE. An independent and blinded analysis of the IVUS images was conducted by a different IVUS core lab (SAHMRI, Adelaide Australia). In this post-hoc but blinded reanalysis, the 3 mg/kg treatment group showed consistent improvement relative to baseline and was numerically superior to placebo in all analysis populations. In the Modified Per Protocol analysis, statistical significance of 3 mg/kg over placebo was achieved for some of the IVUS measurements (7).

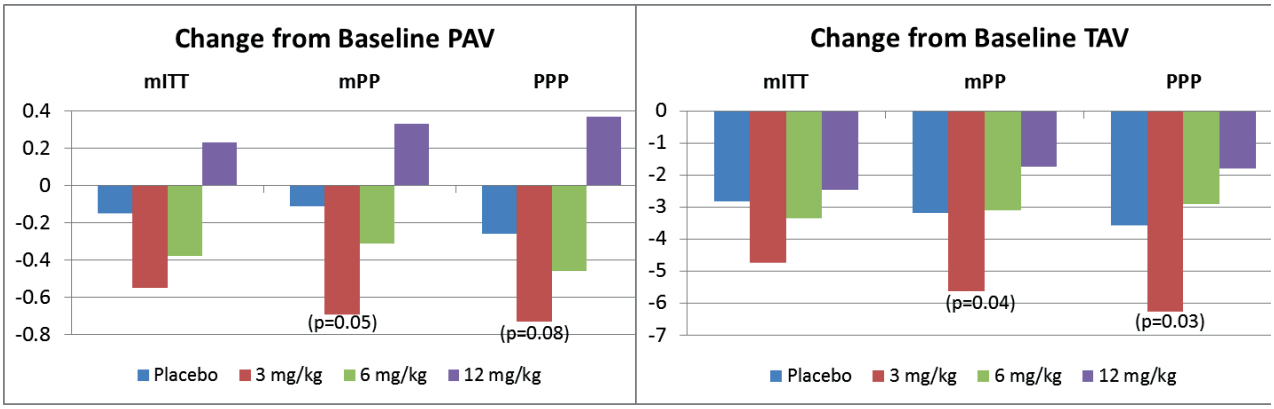

Figure 1. Change in IVUS parameters by treatment group and analysis population
(LS Means from ANCOVA modeling with nonparametric testing due to non-normality of data; mITT = modified intent-to-treat, mPP = modified per-protocol population; PPP = per protocol population)

In general, CER-001 and placebo had a similar safety profile. The incidence and type of SAEs were similar for CER-001 and placebo, with the possible exception of infusion reactions (drug hypersensitivity reactions, anaphylaxis, and adverse drug reactions).

A Phase II study in Homozygous Familial Hypercholesterolemia (HoFH) called MODE has also been completed (18). It was an open-label, single arm active treatment study that enrolled 23 patients. The primary efficacy endpoint was the percent change from baseline to follow-up in carotid artery mean vessel wall area (MVWA). CER-001 produced a clinically meaningful and statistically significant decrease, from a mean of 17.23 mm^2 at baseline to 16.75 mm^2 at Month 6 (2.53%; p=0.0124) in the mITT population (n=18: patients with baseline and follow-up 3T-MRI data). Similar results were seen in the secondary efficacy parameters measuring the effect on the carotid artery. CER-001, administered bi-weekly at a dose of 8 mg/kg for up to 12 months, was well tolerated in these patients. There was only one report of a treatment-related SAE, an urticarial reaction which resolved rapidly with treatment (7).

Importantly, a Phase II study in Familial HDL-C Deficiency also referred to FPHA, called SAMBA, has also been completed. It was an open-label, single arm active treatment study that enrolled nine patients with mutation in ApoA1 and/or ABCA1 gene. The primary study objective was to determine whether the pharmacokinetic and pharmacodynamics behavior of CER-001 was the same in patients with genetic defects affecting the reverse lipid transport pathway. Secondary and exploratory efficacy parameters included measurements of carotid and aortic plaque structure by MRI, carotid plaque inflammation by PET-CT, and fecal elimination of sterols and bile acids. Results from the seven patients who had adequate collection of follow-up data have recently been published (17). The encouraging trial data demonstrated that CER-001 regresses carotid artery inflammation and atherosclerosis and increased elimination of cholesterol from the body. No SAEs were reported nor did any patient discontinue therapy due to an AE. Blood chemistry and hematology findings were unremarkable for this patient population (7).

Recently, the LOCATION study showed that CER-001 is able to target the atherosclerotic carotid plaques in patients with advanced carotid stenosis (*manuscript under preparation*).

3.3.3 Description and Mechanism of Action of CER-001

CER-001 is a complex consisting of recombinant human ApoA-1 and a proprietary combination of charged phospholipids. It is designed to mimic the action of natural nascent, discoidal pre-βHDL particles. When injected intravenously, CER-001 is likely to have properties that are similar to newly synthesized endogenous HDL, which is very effective in mobilizing cholesterol from peripheral tissues. More detailed information on CER-001 is provided in the Investigators' Brochure (IB), 5th version, March 2015 (7).

3.4 Study rationale

The encouraging efficacy results seen to date from the CHI SQUARE (ACS), MODE (FH), LOCATION (carotid stenosis) and most importantly SAMBA (FPHA) studies indicate a potential for CER-001 to bring substantial benefit to patients with FHPA. Despite the efforts made on diet control and aggressive LDL-cholesterol (LDL-C)-directed pharmacotherapy, FHPA patients are remaining at high risk for developing cardiovascular event and there is no treatment currently available, which can directly restore functional HDL. Therefore CER-001 represents a potential treatment for those patients and warrant further clinical studies.

This phase III study will confirm whether or not administration of CER-001 will benefit patients with FPHA.

4 TRIAL OBJECTIVES

4.1 Primary Objectives

The primary objectives of the study are:

- To evaluate the effect of 24 week treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA) as compared to placebo using 3T magnetic resonance imaging (3T-MRI);
- To evaluate the safety and tolerability of CER-001 administered for 24 weeks.

4.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the effect of 8 week and 48 week treatment with CER-001 on MVWA as compared to placebo using 3T-MRI;
- To evaluate the effect of 8 week, 24 week and 48 week treatment with CER-001 on femoral artery as compared to placebo using 3T-MRI;
- To evaluate the effect of 24 week treatment with CER-001 in the target (plaque) to background (blood) ratio (TBR) from an index vessel (either right carotid or left carotid) based on the standardized ^{18}FDG uptake measured with PET/CT.
- To evaluate safety and tolerability of 48 week treatment with CER-001.

4.3 Exploratory Objectives

The exploratory objectives of the study include:

- Evaluate the effect of treatment with CER-001 with respect to other efficacy measurements including carotid artery and carotid normalized wall index using 3T-MRI;
- Evaluate the effect of treatment with CER-001 with respect to potential surrogate markers on vessel wall biology including laboratory variables;
- Evaluate the effect of treatment with CER-001 with respect to inflammation;
- Evaluate plasma-mediated cellular Cholesterol efflux capacity;
- ApoA-1 levels (pharmacokinetic parameters);
- Cholesterols, triglycerides, lipids, apolipoprotein and lipoprotein levels (pharmacodynamics parameters).

4.4 Other Objectives

Other objectives of the study include:

- To evaluate safety and tolerability of 72 week treatment with CER-001.
- To evaluate the effect of 72 week treatment with CER-001 on MVWA using 3T-MRI;
- To evaluate the effect of 72 week treatment with CER-001 on femoral artery using 3T-MRI;

5 RISK BENEFIT STATEMENT

All patients enrolled in this study will have four 3T-MRI measurements during a time period of 48 weeks. 3T-MRI is a non-invasive imaging technique that does not involve exposure to ionizing radiation. The magnetic field itself is not harmful; however, imbedded metallic fragments such as shrapnel or implanted medical devices that contain metal such as pacemakers may malfunction or cause problems during an MRI exam.

Patients in this study will have two ^{18}FDG-PET scans during the study, the first one will be performed at baseline and the second and last assessment will be done at week 24. ^{18}FDG-PET is routinely used in clinical practice. The total radiation exposure in the study corresponding to the two ^{18}FDG-PET CT scans is 9.4 milli-Sievert. Labelled glucose, ^{18}F-deoxyglucose, has no known side effects. No adverse effects are expected.

Two thirds of the patients randomized in the trial will receive twenty-nine infusions of CER-001 (8mg/kg) and one third will receive twenty-nine infusion of placebo. More than 400 patients have been exposed to CER-001 in previous clinical trials including 122 patients exposed to 12 mg/kg CER-001 in phase II study. Overall CER-001 has been well tolerated. The incidence and type of SAEs were similar for CER-001 and placebo, with the possible exception of infusion reactions which occurred more frequently with CER-001 and may occur more frequently at higher doses. These reactions were reversible in all cases and either resolved spontaneously or after management with antihistamines, steroids and/or IV fluids. A phase II study (CARAT) aiming to enroll 292 patients for evaluating the potential benefit of CER-001 in ACS patients is currently ongoing.

6 STUDY DESIGN

6.1 Overview of the study design and dose regimen

This is a Phase III, multi-center, randomized, 48 weeks, double-blind, parallel-group, placebo-controlled study to evaluate efficacy and safety of CER-001 on ApoA-1 and vessel wall area in patients with genetically defined familial primary hypoalphalipoproteinemia and receiving background optimized lipid therapy.

Double-blind treatment phase: After obtaining written informed consent and provided the patient fulfills the selection criteria as defined in *section 7*, he/she will be randomized to receive twenty-nine doses of CER-001 or placebo, weekly during the first 8 weeks (9 doses) and then every two weeks during the following 40 weeks (20 doses). Dosing visits will have a window of +/- 2 days around the strict weekly or biweekly date.

Open-labeled treatment phase: After obtaining written informed consent, patient will receive twelve doses of CER-001, one every two weeks during 24 weeks following the last dose administered during double-blind treatment period. Dosing visits will have a window of +/- 2 days around the strict biweekly date.

Patients will have a safety follow-up visit at least 30 days after the last dose administered.

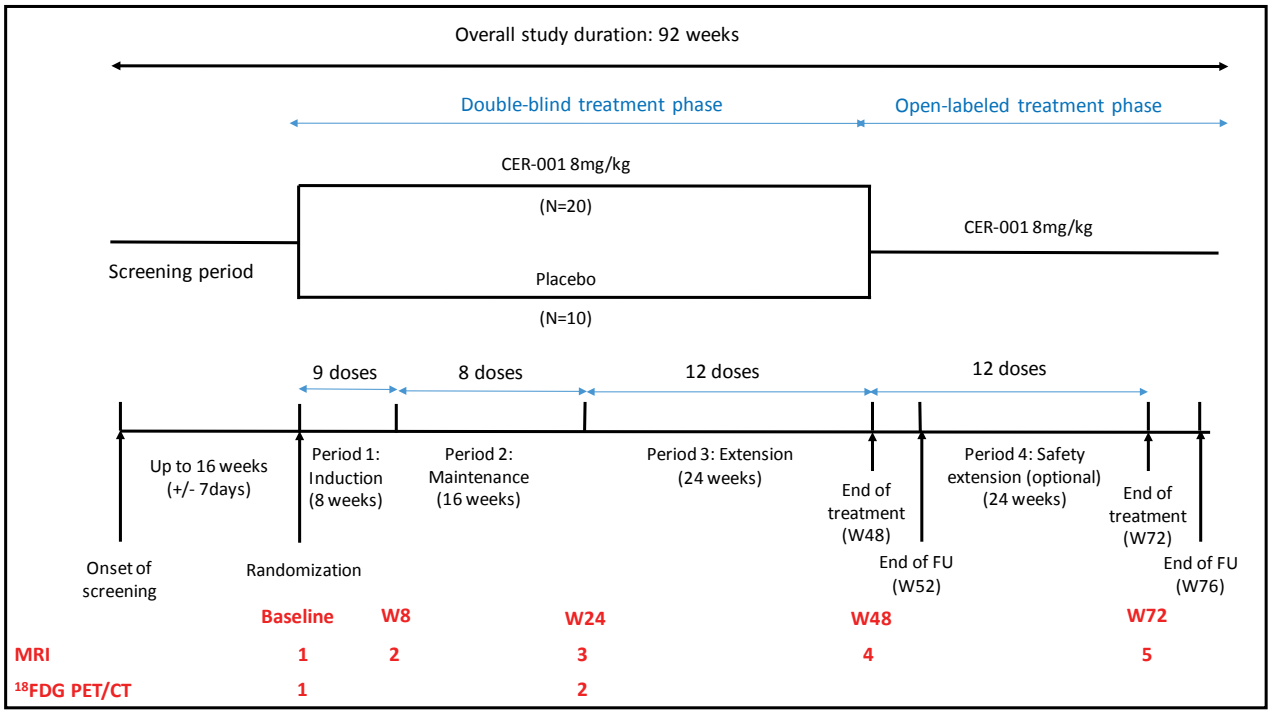

Figure 1. Schematic study design.

6.1.1 Study periods

The study duration can be up to 68 to 92 weeks in total:

- Screening period: up to 16 weeks (+/-7 days)
- Treatment period: the overall treatment period is 48 weeks (+/- 7 days) including an induction treatment phase of 8 weeks, followed by a 16 week maintenance treatment phase and a 24 week extension treatment phase.
- Safety follow-up period: 4 weeks (+/- 7 days) after the end of treatment OR
- Safety extension follow-up: 24 weeks (+/- 7 days) AND Safety follow-up period: 4 weeks (+/- 7 days) after the end of treatment

6.1.2 Rationale for the study design

In the present study, CER-001 will be evaluated at 8 mg/kg dose as its potential to induce regression of carotid atherosclerosis in patients with FPHA. As already described, both MODE (18) and SAMBA (17) studies have proven this dose as efficacious especially in the population addressed in this study (See section 3.3.2. Clinical Findings for CER-001).

Both previous trials mentioned above were designed to address the efficacy of CER-001 at 6 months. Indeed, even though infusion of CER-001 was leading to early positive effect on carotid atherosclerotic plaque burden as detected by a significant reduction of the mean carotid vessel wall area after 1 month treatment (17), it is of main interest to measure the longer lasting effect of the study drug and maintenance of its positive treatment outcome on atherosclerotic plaques. Therefore this study has been designed to confirm the previous clinical evaluation. Moreover, the 24 week extension treatment period (See *Figure 1*) will allow to assess even further beneficial effect of 8 mg/kg dose of CER-001 as well as better evaluating the safety profile of the study drug by collecting safety data from the patients with FPHA exposed to CER-001 for 48 weeks. A final safety visit will occur at week 52.

6.2 Dose and Dose Regimen Selection

Overall CER-001 has shown its potential benefit in various patient populations. Patients receiving 8 mg/kg dose of CER-001 in the MODE study (18) indicate that six months biweekly infusion of CER-001 at 8 mg/kg is beneficial in regressing carotid plaque in patients with Homozygous FH who were receiving optimized LDL-lowering therapy.

Moreover and remarkably CER-001 8 mg/kg transiently restored the population of HDL particles in patients with FPHA in the SAMBA study (17). Cholesterol mobilization was consequently increased along with fecal sterol excretion. CER-001 decreased inflammation in the carotid arteries. CER-001 treatment resulted in plaque regression in the carotids and aorta after 4 weeks of induction therapy and the effect was maintained over six months.

The present study will evaluate the efficacy of 8 mg/kg dose of CER-001 as assessed by 3T-MRI aiming to confirm and validate the benefit on atherosclerosis previously observed in patients with FPHA.

The dose and the dose regimen of the TANGO study are based on the previous positive SAMBA study that included an induction and a maintenance phase.

6.3 End of the study

The study will end when the last randomized patient completes the last assessment 4 weeks after the end of the treatment period.

6.4 Number of patients and assignment to treatment group

A total of 30 patients are planned to be randomized. Treatment groups include 8 mg/kg dose of CER-001 and placebo. Patients will be recruited over a planned recruitment period of 9 months. FPHA is a rare disease explaining the small number considered for this clinical study. The number of patients may slightly increase depending on the ability to find patients with FPHA and a clinical profile matching with the inclusion and exclusion criteria as defined in *Section 7*.

Considering the profile of patients targeted in this study, twice more patients will be randomized into the active 8 mg/kg dose of CER-001 group as compared to those patients who will be randomized into the placebo group - randomization in a 2:1 ratio.

6.5 Centers & countries

Approximately 15 sites from Europe, Canada, United States of America, Brazil and Israel will be involved in this study based on availability of identified patients with this rare disease.

6.6 Safety extension protocol

Patients having completed their last infusion 48 weeks after the first one will be offered to continue in the study for 6 months for safety follow-up.
All patients who accept to continue will be treated with CER-001 8mg/kg whatever the randomization arm. A total of 12 infusions will be administered bi-weekly until week 72. A 3T-MRI scan assessing the carotid and femoral artery will be optimally performed at this visit.
A final safety visit will occur at week 76, 4 weeks after the last infusion.

7 STUDY POPULATION

7.1 Population to be studied

Patients with ApoA-1 ≤ 110 mg/dL and HDL≤ 35 mg/dL with suspected homozygous or heterozygous mutation in the *ABCA1,* and/or *ApoA-1* genes confirmed by genetic testing and background of symptomatic or asymptomatic cardiovascular disease, will be eligible for this study.

Patients, who fulfill all inclusion/exclusion criteria, including confirmation of a genetic defect, may be enrolled in the study.

7.2 Inclusion criteria

A patient may be randomized if the answer to all of the following statements is "yes".

Demographic

1. Male and female patients, aged 18 and above
2. Female patients who are not either surgically sterilized (e.g., tubal ligation or removal of ovaries or uterus) or post-menopausal (no spontaneous menstrual periods for at least one year) must agree to use one of the following forms of contraception from screening until 90 days after the completion of the study medication: (1) systemic hormonal treatment (2) an IUD which was implanted at least 2 months prior to screening or (3) "double-barrier" contraception (condom, diaphragm and spermicide are each considered a barrier), or (4) agree to remain sexually abstinent during the entire study period (when contraception is not acceptable for cultural or religious beliefs)

Procedural

3. Sign written informed consent after the scope and nature of the investigation have been explained to them before screening evaluations and willing to comply with the study restrictions
4. Are fluent in the language of the investigator, study staff (including raters), and the informed consent

Clinical

5. Diagnosis of genetically confirmed HDL-c deficiency due to defects in genes coding for e.g. ABCA1 and/or ApoA-1
6.

IF the subject is on lipid-lowering therapy or NEEDS to be treated with lipid-lowering therapy then the subject must be on a stable dose at least 6 weeks prior to the baseline procedures.

7. Background symptomatic or asymptomatic cardiovascular disease should be present as such:
   - For symptomatic cardiovascular disease: i) history of cardio or cerebrovascular events, ii) diagnosed coronary artery disease (CAD), iii) diagnosed carotid or peripheral stenosis, iv) previous myocardial revascularisation - percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG).
   - For asymptomatic cardiovascular disease: patients with subclinical atherosclerosis diagnosed using imaging method such as i)vDoppler ultrasound, ii)vB-mode ultrasonography – measurement of carotid intima media thickness, iii)vintravascular ultrasonography, iv) Computed Tomography, v) Magnetic Resonance Imaging
8. ApoA-1 ≤ 110 mg/dL
9. HDL-cholesterol ≤ 35 mg/dL or 0.9 mmol/L

7.3 Exclusion criteria

Patients meeting any one of the following criteria are not eligible for the study:

Medical Status

1. Patient with LCAT mutation will be excluded
2. Patient who experienced a cardiovascular event within 6 months prior to the onset of screening
3. Patient who experienced stroke or other cerebrovascular event within 1 year prior to the onset of screening
4. Patient with triglycerides level above 500 mg/dL
5. The patient has evidence of clinically significant, uncontrolled or unstable cardiovascular, renal, hepatic (incl. AST or ALT at or above 3x ULN, or bilirubin at or above 2x ULN), gastrointestinal, hematologic, immunological, neurological, endocrine, metabolic or pulmonary disease (as determined by medical history, clinical laboratory or ECG results, or physical examination) or any other medical disorder that would increase the risk associated with taking study medication or would confound the interpretation of study results
6. Patients with a body mass index (BMI) < 17 kg/m^2 or > 40 kg/m^2
7. Patients with severe anemia defined as hemoglobin level below or equal to 10 g/dL
8. Any clinically significant abnormal laboratory data, vital signs, physical examination at screening or baseline, which in the opinion of the investigator, would interfere with safety assessments

9. Clinically significant electrocardiogram (ECG) abnormality at screening, including sinus bradycardia (resting heart rate < 50 beats per minute), 2nd or 3rd degree atrioventricular block, prolonged QTc (QTcF ≥ 450 ms in males and ≥ 470 ms in females) history of congenital long QT syndromes, or risk of Torsades de Pointes because of family history of sudden death, etc.
10. Positive result on the serum pregnancy test or are breast feeding at screening, or intend to become pregnant during the course of the trial
11. Male intending to father a child during the study
12. Likely to be unreliable as a study participant based on the Investigator's (or designee's) knowledge of the patient (e.g., alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis)
13. Symptomatic (NYHA Class II or greater) congestive heart failure requiring and persisting despite appropriate medical treatment
14. Uncontrolled blood pressure: systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg at screening or any other pre-randomization visit
15. Uncontrolled diabetes mellitus defined as HbA1c >10%
16. Unexplained creatine phosphokinase level > 3 times the ULN
17. History of malignancy during the 3 years prior to screening, with the exception of basal cell carcinoma of the skin
18. Current alcohol or drug abuse or history thereof within 5 years prior to screening
19. Contraindication to MRI scanning such as imbedded metal (e.g., schrapnel), implanted metal objects (e.g., pacemaker), claustrophobia
20. Participated in any investigational study or taken an investigational drug within 30 days (or 5 times the half-life of the investigational drug, whatever is longer)
21. Ever received CER-001within 6 month from the onset of screening
22. Medically non-compliant in the management of their disease in the investigator's opinion

7.4 Concomitant Treatments

Any medication the patient takes, other than study drugs specified by the protocol, is considered a concomitant medication. All concomitant medications must be recorded in the electronic case report form (eCRF).

7.5 Prohibited Medication

There are no excluded medications other than any other investigational drugs.

7.6 Permitted Medication

All medications that are considered medically necessary for maintenance of patient health are permitted during the study. Details of their use must be recorded on the concomitant medication page of the eCRF.

7.7 Monitoring of Patient Compliance

All study therapy will be administered under direct observation.

8 STUDY PROCEDURES

A detailed schedule of assessments by visit is shown in *Appendix A* and Appendix B and a detailed description of assessments and procedures during screening, double-blind and open-labeled treatment is given below.

8.1 Screening Examination and Eligibility Screening Form

All patients must provide written informed consent before any study specific assessments or procedures are performed. An Eligibility Screening Form (ESF) documenting the investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator. A screen failure log must be maintained by the investigator.

Visit 1
This is the first visit of the study. This visit will be performed after obtaining written informed consent. The investigator will advise the patient on heart healthy diet and life style.
Screening assessments include:

- Informed Consent
- Inclusion/exclusion criteria
- Demographic information
- Smoking status
- Measurement of height and body weight
- Medical history/surgical history and concomitant diseases
- Previous and concomitant treatments
- Physical exam (See Section 8.*8*.1)
- Vital Signs (See Section 8.*8*.2)
- Blood Pressure and Heart Rate
- ECG (See Section 8.*8*.3)
- Serum biochemistry (See Section 8.*8*.4)
- Hematology and coagulation (See Section 8.*8*.4)
- Urinalysis (See Section 8.*8*.4)
- Fasting lipid profile (See Section 8.*9*), including Apolipoprotein profile.
- Anti-ApoA-1 antibody (See Section 8.*8*.5)
- Markers of inflammation, oxidation, lipid metabolism and CV risk (See *Section 8.10*)
- Serum pregnancy test in female patients (See Section 11.8)
- FSH (only for women whose last menstrual period was between 6 and 12 months before screening)
- Fasting blood glucose and HbA1c
- Creatinine and/or BUN testing to determine GFR

Patient must have fasted (ie not to take any food or liquids other than water) for 8 hours prior to blood sampling.

A DNA sample will be taken ONLY for determination of the presence of HDL gene mutations specifically for ABCA1 and/or ApoA-1 mutation(s) to ensure that the patient was to satisfy all inclusion and exclusion. Genotyping will be performed at the Robarts Research Institute, London, Canada.

Following visit 1, if a patient is eligible according to all of the inclusion and exclusion criteria, he/she will be instructed to come in fasted for the randomization visit 2.

8.2 Procedures for Enrollment of Eligible Patients and Assessment at Visit 2

Once a patient has fulfilled all inclusion and exclusion criteria, he/she will be randomized at visit 2 to receive CER-001 or placebo using an interactive voice response system (IVRS/IWRS). The investigator/designee will contact the IVRS/IWRS to randomize a patient for this study and will be given a patient number and a randomization number. The investigator or designee will use the eCRF with the assigned patient number and the IVRS/IWRS will automatically download the treatment allocation and randomization number as well as the patient number for the patient into the eCRF.
The following assessments will be performed at visit 2 (V2):

- Physical exam (See *Section 8.8.1*)
- Blood Pressure and Heart Rate
- Measurement of weight and vital signs (See Section 8.*8*.2)
- ECG (See Section 8.*8*.3)
- Blood samples for
  - Hematology and coagulation (See Section 8.*8*.4)
  - Serum chemistry (See *Section 8.8.4*)
  - Fasting lipid profile (See *Section 8.9*)
  - Markers of inflammation, oxidation, lipid metabolism and CV risk (See *Appendix A*)
  - Fasting blood glucose and HBA1c
  - Protein biomarker assessment
- Urinalysis (See Section 8.*8*.4)
- Pregnancy test
- Previous and concomitant medication
- Adverse events
- Creatinine and/or BUN testing to determine GFR

Patient must have fasted (ie not to take any food or liquids other than water) for 8 hours prior to blood sampling.

The first 3T-MRI and the first ^{18}FDG-PET/CT scan assessing the carotid and femoral artery will be optimally performed at this visit prior to the first infusion.

After all assessments have been performed the patient will be administered the first infusion as described in Section 9.6.

He/she will stay for an additional hour after the infusion to ensure completion of the overall examination. A blood sample will be drawn two hours after initiation of the infusion to assess the pharmacokinetics of the study drug.

8.3 Clinical Assessments and Procedures during the Double-blind Treatment Period

Patients will visit the clinic each week for the first 8 weeks and every 2 weeks thereafter until the end of the treatment period (week 48) as described in Appendix A. At each visit, the patient will receive an infusion and will be checked for:

- Adverse events
- Previous and concomitant medications

Complete assessments as described for visit 2 (see *Section 8.2* above) will be performed 4 weeks and 8 weeks after randomization (at visit 6 and visit 10). Thereafter, patients will have complete assessments every 8 weeks until the end of the week 48 treatment period (at week 16, 24, 32, 40 and 48). Unless otherwise specified, blood and urine specimens will be collected prior to study drug dosing.

Markers of inflammation, oxidation, lipid metabolism and CV risk (See *Section 8.10*) will be assessed at baseline, week 8, week 24 and week 48 (end of treatment).

HBA1c assessment will be performed only at baseline (See *Appendix A*).

Anti-ApoA-1 antibody assessment will be performed at week 8, week 24 and week 48 (end of treatment).

Blood samples will be collected for biomarkers assessments at week 24.

A blood sample will also be drawn two hours after initiation of the infusion to assess the PK, at week 24.

Follow-up 3T-MRI will be done at the end of the induction treatment phase (week 8), week 24 and at the end of the overall week 48 treatment period.

Follow-up ^{18}FDG-PET/CT will be performed only once 24 weeks after randomization.

8.4 Clinical Assessments and Procedures during the Open-labeled Treatment Period

Patients will visit the clinic every 2 weeks until the end of the treatment period (week 72) as described in *Appendix B.* At each visit, the patient will receive an infusion and will be checked for:

- Adverse events
- Previous and concomitant medications

Follow-up 3T-MRI will be done at the end of the open-labeled phase (week 72).

8.5 Safety Follow-up

For patients treated until week 48:
Patients will be instructed to fast prior to the visit. A safety follow-up for all patients will be conducted 4 weeks (+/- 7 days) after the final dose of study medication and will include,

- Physical exam (See Section 8.*8*.1)
- Blood Pressure and Heart Rate
- Vital signs (See Section 8.*8*.2)
- ECG (See Section 8.*8*.3)
- Previous and concomitant treatments
- Adverse Events
- Urinalysis (See Section 8.*8*.4)
- Blood samples for
  - Serum biochemistry (See *Section 8.8.4*)
  - Hematology and coagulation (See Section 8.*8*.4)

For patients treated until week 72:
A safety follow-up for the patients will be conducted by phone 4 weeks (+/- 7 days) after the final dose of study medication and will include:

- Previous and concomitant treatments
- Adverse Events

8.6 Specific Imaging Assessments

8.6.1 Assessment of Vascular Structure of the Carotid and Femoral with 3T-MRI

Patients will have 3T-MRI imaging performed at Baseline, Week 8, Week 24, Week 48 and Week 72 (optional) for carotid and femoral Mean Vessel Wall Area (MVWA) and carotid normalized wall index (NVWI) measurements.

The baseline 3T-MRI can be done anytime during the screening period, before the randomization provided all other selection criteria are satisfied.

All images will be collected for their review by an imaging expert, with a window of +/-7 days around the strict date.

The detailed procedure for performing and collecting of 3T-MRI images will be outlined in the Imaging Manual.

8.6.2 Assessment of target (plaque) background (blood) ratio with PET/CT

Patients will have two PET/CT scans with labelled glucose ^{18}F-deoxyglucose at Baseline and Week 24 only at the sites appropriately equipped.

The baseline PET/CT scan can be done anytime during the screening period, before the randomization.

All images will be collected for their review by an expert, with a window of +/-7 days around the strict date.

The detailed procedure for performing and collecting PET/CT scans will be outlined in the Imaging Manual.

8.7 Assessments and Procedures for Patients who Prematurely Discontinue Study Medication during double-blind treatment period

Patients who withdraw from study medication should come to the site for a safety follow-up, 4 weeks after the last dose: the same safety assessments as the ones planned for study completer's week 52 visit (V31) should be performed.

Additionally:

- In case the study medication is stopped prematurely prior to week 24 (V18), a 3T-MRI should be performed as soon as possible after study drug discontinuation. If the patient agrees to stay in the study, he/she will be asked to come back at the site for full assessments as per protocol every 8 weeks until visit V30 and a last 3T-MRI will be performed at visit V30.
- In case the study drug is stopped during the extension treatment period (i.e. after week 24 (visit V18), patient should come back to the site for full assessments as per protocol every 8 weeks until week 48 , a last 3T-MRI will be done at week 48.

All AEs (related or not related) must be reported until the final study evaluation at visit V30 and thereafter only the SAEs likely to be related to the study drug or study procedures must be notified.

8.8 Assessment of Safety

During double-blind treatment period, all patients who receive at least one dose of study medication and have a subsequent safety evaluation will be included in the safety analyses.

Safety assessments will include:

- Physical exam
- Vital signs assessments
- Electrocardiogram (ECG) assessments

- Laboratory tests
- Adverse events (AEs)
- Metabolic parameters
- Urinalysis
- Anti-ApoA-1 antibody

During open-labeled treatment period, all patients who receive at least one dose of CER-001 and have a subsequent safety evaluation will be included in the safety analyses.

Safety assessments will include Adverse Events (AEs).

8.8.1 Physical Exam

The Investigator or qualified designee will perform a complete physical examination at Screening, Baseline, week 4, week 8 and every 8 weeks until the end of treatment. Additionally, a last physical examination will be done at the end of follow-up visit. Height will be collected at the screening visit only. The complete physical examination should include assessment of general appearance, HEENT/neck, pulmonary system, cardiovascular system, abdomen, extremities, musculoskeletal system, neurological system, and skin. Any findings that differ from the screening visit will be noted and if adverse and clinically significant, in the judgment of the Investigator, will be reported on the adverse event form.

8.8.2 Vital Signs

Temperature in degree centigrade and respiratory rate (RR) should be measured at the screening visit, randomization, at week 4, week 8 and every 8 weeks until the end of treatment. Additionally, assessment of vital signs will be done at the end of follow-up visit. Respiratory rate should be measured by counting the number of respirations for 30 seconds, and then multiplying by 2 in order to obtain the RR per minute. The patient's pulse should be measured for 30 seconds, and then multiplied by 2 in order to obtain HR per minute.

Blood pressure (BP) and heart rate (HR) should be measured at screening visit, randomization, pre-infusion and post-infusion (after the post-infusion observation period prior to the patient leaving the clinic) at week 4, week 8 and every 8 weeks until the end of treatment. Additionally, a last BP assessment will be done at the end of follow-up visit. BP and HR measurements should be determined after the patient has been seated for at least 5 minutes. At the screening visit, the BP will be measured twice in each arm in order to determine the arm to use for subsequent measurement (unless a concomitant condition favors the use of a particular arm), using an appropriately sized cuff. The second BP measure should be taken at least 2 minutes following the first measure. The arm with the higher average systolic reading will then be used for single determinations of BP throughout the remainder of the study. If patient has a systolic blood pressure (SBP) reading of >160mmHg at time of randomization the Investigator, in consultation with the patient may measure again if able to randomize within the allowed window.

8.8.3 Electrocardiograms

Protocol-specified ECGs will be acquired. 12 lead ECGs will be performed using equipment on site at screening visit, randomization, week 4, week 8 and every 8 weeks until the end of treatment. Additionally, a last ECG will be done at the end of follow-up visit. The Investigator will perform standard interpretations of all tracings with results documented in the appropriate source documents and CRFs.

It is the responsibility of the Investigator to obtain additional ECGs required for the clinical management of the patient. All ECGs supporting any suspected MACE or other SAE/AE during the course of the study period, wherever performed, will be reported in the eCRF.

8.8.4 Clinical Laboratory Tests

Laboratory tests should be measured at the screening visit, randomization, at week 4, week 8 and every 8 weeks thereafter until the end of treatment. Additionally, laboratory tests will be done at the follow-up visit. Any blood sample collected according to the Schedule of Assessments (Appendix A) may be analyzed for any of the tests outlined in the protocol. This may also include, but is not limited to, investigation of unexpected results and incurred sample reanalysis.

Clinical laboratory safety testing during the screening and treatment periods will be performed by a central laboratory. Collection kits, shipment instructions, and a detailed clinical laboratory manual will be provided to the study sites. Investigators are required to review the labs upon receipt and make a determination of clinical significance for labs outside of the normal range. All laboratory reports must be reviewed, signed and dated by a medically trained investigator. Clinical laboratory safety testing will consist of the following panels of laboratory tests. The details of which tests are performed at each visit can be found in Appendix A.

CHEMISTRY PROFILE

Glucose
Blood Urea Nitrogen (BUN)
Creatinine
Total Bilirubin
Indirect Bilirubin
Aspartame Aminotransferase (AST/SGOT)
Alanine Aminotransferase (ALT/SGPT)
Alkaline Phosphatase
Total Protein
Albumin
Lactate Dehydrogenase (LDH)
Creatine Kinase (CK)
Sodium
Potassium

Chloride
Carbon dioxide
Uric Acid
Calcium
Phosphorous

HEMATOLOGY

White Blood Count
Red Blood Count
Hemoglobin
Hematocrit
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

URINALYSIS

Microalbuminuria
Specific Gravity
pH
Glucose
Total Protein
Ketones
Total Bilirubin
WBC
RBC
Casts

The results of all laboratory tests required by the protocol will be documented and will be transferred to the study database via 21 CFR 11 compliant methodology. All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the Investigator and the Medical Monitor, or until a diagnosis that explains them is made.

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are described in *section 11.1*.

A serum pregnancy test will be done at screening visit only. Urinary pregnancy test will be used during the course of the study.

8.8.5 Immunogenicity Testing

Specimen will be collected for anti-ApoA-1 antibody testing at the screening visit, week 8, 24 and end of treatment period. If patients have a positive result for the presence of neutralizing anti-ApoA1 antibody at the end of treatment period visit, the patients must return monthly for testing until the antibodies return to screening value. Collection tubes will be supplied by the central laboratory as part of the visit specific kits for these visits. Collection, processing and shipment instructions will be located in the Laboratory Manual provided to the study sites. The clinical sites will send batch shipments of samples to the central laboratory monthly or sooner depending on local site requirements. An aliquot for specimens that test positive for Anti-ApoA-1 antibody testing will be analyzed for neutralizing antibody activity.

8.9 Assessment of Lipid Profiles

Fasting* samples for the following lipid profile tests will be obtained at screening visit, baseline, week 8, week 24 and week 48:

- Total Cholesterol
- Unesterified Cholesterol
- Esterified Cholesterol
- LDL Cholesterol
- HDL Cholesterol
- Triglycerides
- Phospholipids
- Apolipoprotein A-1, Apolipoprotein B
- Apolipoprotein profile

*Patient must have fasted (ie not to take any food or liquids other than water) for 8 hours prior to blood sampling.

Assessment of Lipid Profiles will be performed by a central laboratory. Instructions for the collection, storage and shipment of lipid profile samples will be included in the laboratory manual. There will be no data reporting to the Investigator or the Sponsor for lipid profiles prior to database lock with the exception of screening triglyceride values and any triglyceride value greater than 1000 mg/dL.

8.10 Assessment of Markers of Vessel Wall Biology

Blood samples will be obtained at screening visit, baseline, week 8, week 24 and week 48 visits to analyse markers on vessel wall biology including and not restricted to laboratory variables such as absolute and relative change in high sensitivity C-reactive protein (hs-CRP), PON-1, MMP-9 and other selected inflammatory markers (TNFα, IL-6), soluble VCAM-1 , sMCP1, Oxysterols (FACS Analysis), ABCA1 mRNA and protein levels (Monocytes).

Instructions for the collection, storage and shipment of samples will be included in the laboratory manual.

8.11 Assessment of Cellular Cholesterol Efflux

Blood samples will be obtained at screening visit, baseline, week 8, week 24 and week 48. At infusion visits, samples should be drawn 2 hours after the start of the infusion.

8.12 Assessment of Biomarkers

Plasma samples will be obtained at baseline and week 24.

Instructions for the collection, storage and shipment of samples will be included in the laboratory manual.

8.13 Efficacy Assessment of Procedures

8.13.1 Primary Efficacy Parameters

The primary efficacy parameter of this study will be the change from baseline after 24 weeks treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA) as compared to placebo using 3T-MRI when administered to patients with FPHA.

8.13.2 Secondary Efficacy Parameters

The secondary efficacy parameters will be to evaluate the:

- Change from baseline after 8 week and 48 week treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA) as compared to placebo using 3T-MRI when administered to patients with genetically defined FPHA
- Change from baseline after 8, 24 and 48 week treatment with CER-001 on femoral artery as compared to placebo using 3T-MRI when administered to patients with genetically defined FPHA
- Change from baseline at 24 weeks in the target (plaque) to background (blood) ratio (TBR) from an index vessel (either right carotid or left carotid) based on the standardized ^{18}FDG uptake measured with PET/CT in patients with genetically defined FPHA.

8.13.3 Exploratory Efficacy Parameters

- Evaluate the effect of treatment with CER-001 in patients with genetically defined Familial Primary Hypoalphalipoproteinemia (FPHA) with respect to other efficacy measurements including carotid artery and carotid normalized wall index using 3T-MRI
- Evaluate the effect of treatment with CER-001 in patients with genetically defined Familial Primary Hypoalphalipoproteinemia (FPHA) with respect to potential markers on vessel wall biology including and not restricted to laboratory variables such as absolute and relative change in high sensitivity C-reactive protein (hs-CRP), MMP-9 and other selected

inflammatory markers (TNFα, IL-6), PON-1, soluble VCAM-1 and sMCP1, plaque characterization indexes using 3T-MRI
- Evaluate Plasma-mediated cellular Cholesterol efflux capacity.

8.13.4 Other Efficacy Parameters

- Change from baseline after 72 week treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA) using 3T-MRI when administered to patients with genetically defined FPHA
- Change from baseline after 72 week treatment with CER-001 on femoral artery using 3T-MRI when administered to patients with genetically defined FPHA

8.14 Safety Assessments

8.14.1 Primary safety parameter

The primary safety parameter will be to:
- Evaluate safety and tolerability of CER-001 administered for 24 weeks

8.14.2 Secondary safety parameters

The secondary safety parameter will be to:
- Evaluate safety and tolerability of CER-001 administered for 48 weeks

Safety parameters will also be evaluated as secondary endpoints and will include:
- Incidence and severity of AEs from routine monitoring
- Incidence of abnormalities and changes from baseline in clinical laboratory parameters from testing of blood and urine, including antibody development

8.14.3 Other safety parameters

Other safety parameter will be to:
- Evaluate safety and tolerability of CER-001 administered for 72 weeks

Safety parameters will include:
- Incidence and severity of AEs from routine monitoring.

8.15 Protein Biomarker Study

Specimens for protein biomarker discovery and validation will be collected from all patients. These specimens will be used for research purposes ONLY to identify and/or verify biomarkers that are

linked to CER-001 treatment and could help to understand the pathogenesis, course and outcome of the disease of the targeted patient population. These samples will be used to measure soluble serum proteins that could potentially correlate with response to treatment with CER-001. Identification of patient subgroups with an increased or decreased response to therapy (homozygous versus heterozygous mutations in ABCA1 and/or APOA-1 gene) may provide information of significant clinical value to guide treatment decisions and aid in the appropriate use of the therapy.

For sampling procedures, storage conditions and shipment instructions see laboratory instruction manual. These specimens will be stored for 5 years and then destroyed.

8.16 Pharmacokinetic (PK) parameters

Two PK samples will be taken 2h after starting the infusion administration, after the first infusion administration (V2) and at Week 24 (V18).

9 INVESTIGATIONAL MEDICINAL PRODUCT

9.1 Dose and Schedule of Test "Drug" and Placebo

Patients will be administered 8 mg/kg dose of CER-001 or a matching placebo infusion once weekly for 8 weeks and every 2 weeks thereafter. Study medication will be administered at the site by qualified staff.

9.2 Pharmaceutical Properties and Formulation

The study drug, CER-001 Sterile Solution for Infusion, is a solution of the ApoA-1/phospholipid complexes in phosphate-buffered solution with sucrose and mannitol. The calculated concentration of CER-001 complexes is based on protein content (8 mg/mL). The CER-001 Sterile Solution for Infusion is filled into 20 mL glass serum vials (17.2 mL minimum extractable volume), stoppered with grey butyl rubber stoppers and sealed with aluminium crimp seals.

Study drug product will be diluted with normal saline to accommodate the dosing range. CER-001 solution will be supplied and stored frozen, to be thawed and diluted prior to administration at the study site. Thawing and dilution procedures will be detailed in a Pharmacy Manual for the study. A general description of CER-001 product is provided in *Table 1*.

Table 1 Pharmaceutical Properties of CER-001

International Non-Proprietary Name (INN)	Recombinant human apolipoprotein A-1
United States Adopted Name (USAN)	To be determined
CAS Number	1383435-67-3
Laboratory Code	CER-001
Description (Drug Substance)	Protein/phospholipid complex containing a 1:2.7 weight to weight ratio of recombinant human ApoA-1 to phospholipids (97% Sph, 3% DPPG)
Physical Form (Drug Product)	Solution of the ApoA-1/phospholipid complexes in phosphate buffered solution with sucrose and mannitol (10 mM phosphate buffer, 4 % sucrose, 2% mannitol, pH 8.0). Protein content 8mg/mL.
External Appearance	Frozen solution (17.2mL extractable volume) in 20 mL glass vials with 20 mm gray butyl rubber stoppers, sealed with 20mm aluminium crimp seals with red flip-off caps
Storage Conditions	Store frozen at -15C to -25C; thaw before administration. A matching placebo of normal saline will also be supplied.

9.3 Placebo

Placebo, standard sodium chloride solution, is provided as a 250 mL solution for infusion similar in volume to the active treatment solution study.

9.4 Packaging and Labelling

The packaging and labelling for all study medication will be performed by Catalent Pharma Solutions for Cerenis Therapeutics and will comply with local applicable regulations. Labelling requirements for the dispensed IV containers will be specified in the Pharmacy Manual.

9.5 Medication Dispensing and Administration

The Investigator will administer the study medication only to patients included in this study following the procedures set out in the study protocol. Each patient will be given only the study medication assigned by the randomization system. All dispensing will be documented in the eCRF and other study drug records.

9.6 Method of Administration

CER-001 is provided as a frozen solution in 20 mL vials containing at least 17.2 mL of product at a concentration of 8 mg/mL (ApoA-1 content).

CER-001 will be constituted into an IV dosing solution by the Study Pharmacist or designee by diluting with normal saline. All doses will be diluted with normal saline to a volume of 250 mL and will be administered over a one-hour period using an infusion pump at a fixed rate of 250 mL/hr. Study drug administration may be extended up to a period of 120 minutes if deemed medically necessary for the patient by the Investigator (e.g. concern for fluid overload). Reasons for administration periods greater than 60 minutes must be properly documented. Patients should be observed for a minimum of 15 minutes following the infusion.

Placebo, standard 250 mL sodium chloride solution, is provided and will be administered over a one-hour period using an infusion pump at a fixed rate of 250 mL/hr.

Patients should be observed for a minimum of 15 minutes following the infusion.

The Study Pharmacist or designee will dispense the appropriate concentration and volume of solution for each patient, based on his/her weight at Screening. The infusion bag and drip set will be sent from the pharmacy with the infusion bag shrouded with a bag to maintain the blind.

9.7 Additional Supplies Provided by Sponsor

IV bags, tubing and infusions pumps will be supplied by the sponsor as necessary.

9.8 Investigational Product Accountability

The Investigator or designee must maintain accurate and adequate records including dates of receipt and return of drug shipments, lot number (if available), and quantities received/returned, as well as dates and amounts administered, and returned by the study site.

All vials, empty, partial, or full, must be returned. The study site must ensure that unused supplies remain in their original containers as provided by Catalent Pharma Solutions for Cerenis Therapeutics and that the label is intact and unobliterated. The “Clinical Returns Authorization Form” contains a specific return shipping address and instructions.

9.9 Randomization

After obtaining written informed consent, completing screening procedures, and ensuring the patient meets all of the inclusion criteria and none of the exclusion, the patient will then be randomized. Stratification according to the genetic mutation will be done to ensure appropriate balanced

distribution of the mutations across treatment groups. The patient will be randomized to receive 29 infusions of either active drug or placebo; 2:1 randomization scheme will be used as indicated in section 6.1.

9.10 Treatment Blinding

Study drug will be dispensed by an unblinded Study Pharmacist or designee. Study drug blinding to the Investigator and all other staff at site will be achieved by shrouding the IV container with an opaque bag, sealed by the pharmacist. Any labelling necessary for administration will be affixed both to the IV container and to the shroud itself. The Study Pharmacist will be responsible for ensuring consistency of the labels. After administration, the infusion bag will be returned within its shroud to the pharmacy. After the last patient completes the final visit, the database will be cleaned and locked after this data is entered, and the data will be unblinded and analyzed for all primary and secondary efficacy and safety parameters.

9.11 Maintaining the Blind

Study drug will be dispensed by an unblinded Study Pharmacist or designee who will be unblinded as described in Section above (Section 9.10). The study patients, Investigator, sponsor and study site personnel and site monitors will remain blinded to the treatment. During the study, and prior to database lock, no lipid profile data will be reported to the Investigator or to the Sponsor. Data will be reviewed in a blinded manner.

Randomization list is kept strictly confidential, accessible only to authorized persons, until the time of unblinding. It is the responsibility of the Pharmacist to maintain the blind throughout the study.

The randomization code may be broken if an emergency situation arises that in the Investigator's opinion requires the knowledge of the code (for example, life threatening situation or necessity to know the product administered to provide with the best medical care). The investigator must do his/her very best to contact the Sponsor before unblinding the code using an Interactive Web Response System (IWRS). Date, time, and reason(s) for breaking the code must be recorded by the Investigator in IWRS.

At the conclusion of the trial, the occurrence of any emergency code breaks will be verified after return of all code break reports and unused drug supplies to the packaging supplier.

The CRO mandated for pharmacovigilance reserves the right to break the blind for SAEs which are considered as related to the study drug and unexpected, which could require an expedited report to the regulatory authorities.

9.12 Withdrawal From Study Participation

Reasons for withdrawal from study drug may include, *but are not limited to*, the following:

- Investigator's request, for safety reasons, such as severe adverse reactions
- Investigator's request, for other reasons, such as patient non-compliance
- Patient's request, for tolerability reasons
- Patient's request, for other reasons, such as withdrawal of informed consent

Discontinuation of study drug alone does not constitute discontinuation or withdrawal from the study.

Patients should continue to be followed as though they had completed the treatment phase. Patients who prematurely discontinue study medication are to be followed as described in the *section 8.7*.

All premature study discontinuations and their causes must be carefully documented by the Investigator.

A discontinuation occurs when an enrolled patient ceases participation in the study, regardless of the circumstances, prior to completion of the final protocol procedures. The Investigator must determine the primary reason for discontinuation. Withdrawal due to an adverse event should be distinguished from withdrawal due to other reasons according to the definition of adverse event (See Section 11.1). A discontinuation must be reported immediately to the Sponsor (or designated representative) if it is due to a serious adverse event (see *Section 11.5*).

If a patient discontinues treatment, the Investigator will record the reason for study drug discontinuation, provide or arrange for appropriate follow up for such patients, and document the course of the patient's condition during the appropriate follow up period on the follow up contact eCRF.

Patients who withdraw consent and refuse to return for subsequent visits, if consent to, will be contacted by telephone within 30 days following last study drug administration to assess their current health status. It is imperative that all patients are accounted for at the conclusion of the trial.

10 TREATMENT OF PATIENTS

10.1 Study Drug Administration

The first dose administration will occur at the randomization, first infusion visit (visit 2), and weekly scheduled visits for the first nine doses induction period. During the maintenance and extension periods, dosing will occur every 2 weeks for the following twenty doses until the end of the week 48 treatment period.

At each of these visits, patient will be given a single intravenous infusion of either placebo or CER-001 (8mg/kg) over a one hour period. Dosing procedures are specified in Section 9.6 (Method of Administration).

10.2 Interruption or Discontinuation of Study Medication

Patients may be interrupted or discontinued from study medication if any of the following occur:

1. Any drug-related adverse event or other reason which, in the Investigator's opinion, will jeopardize the patient's participation in the trial or the interpretation of trial data (e.g., severe inter-current illness requiring additional care measures or preventing further dosing)
2. Significant tolerability issues

At the time of study medication interruption, the study site will document in the eCRF the reason for drug discontinuation. The patient should continue to be followed clinically and all attempts should be made to re-institute study medication within 21 days of the study drug interruption if not otherwise contraindicated. Study medication may be re-instituted at the initial dose level, or by using a dose reduction scheme as outlined in the following section.

10.3 Dose Adjustments of Study Medication

The Principal Investigator will liaise with the Medical Monitor in relation to potential dose reductions. At the discretion of the Medical Monitor, the dose of study medication may be temporarily or permanently reduced any time after administration of the initial dose (Visit 2). Reasons for dose reduction may include but are not limited to significant tolerability issues.

Dose reductions will always be 50% of the previously administered dose level. Dose reduction may be performed up to two times, i.e. 25% of the original dose.

Dose reduction will be accomplished by preparation of a reduced dose by the Study Pharmacist. Reduced doses will still consist of a total of 250 mL of study drug solution to be administered over 60 minutes. Complete instructions for preparation of reduced doses will be contained in the Pharmacy Manual.

The investigator may increase the patient dose back up to the prescribed dose in consultation with the studies medical monitor. All dose increases should be accomplished by doubling the previously administered dose. In no case should the patient receive a dose greater than the prescribed dose.

11 SAFETY MONITORING

11.1 Definitions

Adverse Event (AE): An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during a study are to be reported as AEs.

In clinical studies, an AE can include an undesirable medical condition occurring at any time, including screening or wash-out periods, even if no experimental treatment has been administered.

Treatment Emergent Adverse Events (TEAE): Treatment emergent adverse events are defined as adverse events which occur during or after the administration of the first dose of the investigational medicinal product (IMP) or if present before the first administration of IMP, worsen on study treatment.

Adverse Drug Reaction (ADR): An adverse drug reaction is any untoward and unintended response to a medicinal product related to any dose administered.

Unexpected Adverse Drug Reaction: Any adverse drug reaction the nature, severity or outcome of which is not consistent with the applicable product information.

In this study, the reference document to be used to evaluate the unexpectedness of the adverse drug reactions consists in *section 5.7* Possible Adverse Reactions" of the Investigator's Brochure (most recent version).

Events involving illnesses with onset during the study, or exacerbation of pre-existing illnesses should be recorded as adverse events. Exacerbation of pre-existing illness is defined as a manifestation (sign or symptom) of the illness that indicates a significant increase in the severity of the illness as compared to the severity noted at the start of the trial. It may include worsening or increase in severity of signs and symptoms of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/complication. Exacerbation of a pre-existing illness should be considered when a patient requires new or additional concomitant drug or non-drug therapy for the treatment of that illness during the trial. In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., laboratory, x-ray, ECG) should also be recorded as adverse events.

Laboratory test abnormalities & follow-up

Laboratory test results will be recorded on the laboratory results eform of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE form in the eCRF:

- Accompanied by clinical symptoms
- Test result requiring additional diagnostic testing or medical/surgical intervention,
- Leading to a change in study medication (e.g. interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study medication, which falls outside the laboratory reference range and meets the clinical significance criteria.

This does not apply to any abnormal laboratory result which falls outside the laboratory reference range but which does not meet the clinical significance criteria (these will be analyzed and reported as laboratory abnormalities); those which are considered AEs of the type explicitly exempted by the protocol; or those which are a result of an AE which has already been reported.

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

11.2 Adverse Event Severity Rating

The severity of an AE will be assessed according to the following scale:

- Mild: Awareness of sign or symptom, but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity
- Severe: Incapacitating with inability to work or perform usual activity

11.3 Relationship to Study Drug

The Investigator should assess the relationship of an AE to study drug according to the following definitions:

Not related:

1. The existence of a clear alternative explanation (e.g., mechanical bleeding at surgical site) or
2. Non-plausibility, e.g., the patient is struck by an automobile or cancer developing a few days after drug administration.

Unlikely (remote):
A clinical event, including laboratory test abnormality (if applicable), with an improbable time sequence to drug administration and in which other drugs, chemicals or underlying disease provide plausible explanations.

Possible:
A clinical event, including laboratory test abnormality (if applicable), with a reasonable time sequence to administration of the drug, which could also be explained by concurrent disease or other drugs or chemicals.

Probable:
A clinical event, including laboratory test abnormality (if applicable), with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.

Definite:
A clinical event, including laboratory test abnormality (if applicable), for which there is no uncertainty in the relationship to test product administration (e.g., positive recalling).

11.4 Adverse Event Reporting

All observed or volunteered adverse events occurring during the study period, at any time from the signature of the informed consent until the final study evaluation, regardless of treatment group or suspected causal relationship to study drug, will be recorded on the adverse event page(s) of the eCRF.

The need to capture this information is **not dependent** upon whether the adverse event is considered to be related to the use of the study drug. Also, adverse events resulting from concurrent illnesses and reactions to concurrent medications must be reported. In order to avoid vague, ambiguous, or colloquial expressions, the AE will be recorded using standard medical terminology rather than the patient's own words.

Each AE should be described in detail in the eCRF: nature of the event (a sign, a symptom or a diagnosis preferably), onset and stop dates, severity, relationship to study drug, seriousness (see below *Section 11.5*), action taken including corrective therapy and outcome.

AEs that are believed to be at least possibly related to study drug should be followed until satisfactory resolution or acceptable stabilization.

For all AEs, the Investigator must pursue and obtain the necessary information both to determine the outcome of the adverse event and to assess whether it meets one of the criteria for classification as a serious adverse event requiring immediate notification to the **PV Department of ICTA PM** (see *Section 11.5*). For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the adverse event (e.g., study drug or other illness).

11.5 Serious Adverse Events

11.5.1 Definition

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

1. Results in death;
2. Is life-threatening;
3. Results in patient's hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability/incapacity; or
5. Results in congenital anomaly/birth defect
6. Is a medically significant event

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse event considered as related to the study drug and which is both unexpected and serious.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient or 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 patient hospitalization, or the development of drug dependency or drug abuse.

A life-threatening adverse event is any adverse event that places the patient at immediate risk of death from the reaction as it occurred (e.g., it does not include a reaction that, had it occurred in a more severe form, might have caused death).

Initial hospitalization is defined as any inpatient admission (even if less than 24 hours). For chronic or long-term in patients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit (e.g., from the psychiatric wing to a medical floor, from a medical floor to the coronary care unit, from the neurological floor to the tuberculosis unit).

Inpatient admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness", is not considered as an adverse event and thus is not subject to immediate reporting. For example:

1. Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
2. Social admission (e.g., patient has no place to sleep)
3. Administrative admission (e.g., for yearly physical exam)
4. Protocol-specified admission during a clinical trial (e.g., for a procedure required by the study protocol)

5. Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery).

The following events are neither considered as inpatient admission nor serious adverse events:

1. Emergency Room/Accident and Emergency/Casualty Department visits
2. Outpatient/same-day/ambulatory procedures
3. Observation/short-stay units
4. Rehabilitation facilities
5. Hospice facilities
6. Respite care (e.g., caregiver relief)
7. Skilled nursing facilities
8. Nursing homes

11.5.2 Reporting

Any SAE, occurring during the study period, at any time from the signature of the informed consent until the final study evaluation, regardless of treatment group or suspected causal relationship to study drug, must be reported by the investigator **within 24 hours** from the date of the first awareness to:

the PV Department of ICTA PM
by email to pharmacovigilance@icta.fr (or by fax: +33 380 539 110)

The Investigator (principal investigator or any other investigator designed by the principal investigator as authorized to notify safety issues) will be requested to complete and sign a separate SAE report form in addition to the information recorded on the adverse event page of the eCRF.
All available information concerning the SAE (copies of laboratory results, other exams, hospitalization reports, autopsy report and other appropriate documents) will be transmitted anonymously with the SAE report form.

Any laboratory result abnormality fulfilling the criteria for a SAE should be reported as such, in addition to being recorded as an AE in the eCRF. As soon as the diagnostic term for the laboratory result abnormality is available, the SAE report should be updated to include the diagnosis as event term, if possible.

In case of SUSAR, the Sponsor or its representative will be responsible for their notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in studies of CER-001 will also be informed as required by regulations.

11.5.3 Follow-up of Serious Adverse Events

For any new information relating to an already notified SAE, the investigator will have to complete a SAE Follow-up report which will be transmitted by fax/email, within **24 hours**, to the **PV Department of ICTA PM to pharmacovigilance@icta.fr (or by fax: + 33 380 539 110)**

accompanied with anonymized copies of the applicable laboratory results, other exams and/or the hospitalization reports.

The reporting of the follow-up information will be done in the same manner as initial SAE reports. Any SAE, regardless of the causal relationship to the study drug, must be followed until satisfactory resolution or stabilization (in case of sequelae) of the event. This can sometimes mean that the follow-up continues after the patient study termination. Satisfactory resolution may include referral to the patients usual care provider.

11.5.4 Serious Adverse Events occurring after the study

All SAEs occurring at any time after the end of the study, likely to be related to the study drug or to a study procedure, according to the investigator, must be notified according to the process for SAE reporting described above.

11.6 Expected Adverse Drug Reactions

CER 001 has previously been administered to humans in single doses ranging from 0.25 to 45 mg/kg. No treatment related AE were reported in that single dose study. In the completed multiple dose studies the adverse event profile has been consistent with what would be expected from the experience of Phase I and Phase II studies and from treating these populations of patients.

AEs that would be reasonable to expect based on repeat dosing in animal toxicity studies include increased liver enzymes, and changes to red blood cell indices although these have not been observed with single or multiple human doses at a rate higher than that observed with placebo. Other AEs that may be anticipated are local injection site reactions and allergic responses. These reactions may include one or more of the following symptoms: wheezing, eye itching, eye swelling, facial swelling, rash , feeling cold, decrease in body temperature, cold sweat, cold shivers , chest pressure, chest pain, jaw pain, decreased blood pressure, increased blood pressure, fatigue, dizziness, headache, nausea, vomiting, stomach pains, and diarrhea.

11.7 Liver and kidney expected adverse reactions which may lead to drug withdrawal

To date, there have been no significant laboratory abnormalities associated with the use of CER-001 in humans, however toxicology studies in mice and monkeys indicate that liver and kidney are possible target organs for toxicity.

Specific requirements for hepatic and renal abnormalities are detailed below.

Hepatic Stopping Criteria:

In the case of Liver Function Test elevation > 3xULN, additional workup may be required within 24 hours of the event by the investigator in close consultation with the Sponsor according to established protocols. This is to rule out possible cases of Hy's law.

Patients should have dosing withheld if the most recently obtained serum ALT or AST exceeds five times the upper limit of normal. If the most recently obtained serum ALT or AST elevation is greater than the upper limit of normal but less than five times the upper limit of normal, the patients may receive their next dose, which may be reduced in consultation with the Sponsor (see *Section 10.3* for more details).

Discontinuation criteria:

Any of the following findings should prompt discontinuation from study drug:

- First observation of ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- Any case of Hy's Law (i.e., ALT or AST >3xULN and TBL >2xULN or jaundice)

All Hy's Law cases (i.e., ALT or AST >3xULN and TBL >2xULN or jaundice) have to be reported as adverse events.

Re-challenge following discontinuation of study drug for either aminotransferase elevations or for potential or confirmed Hy's Law cases must not be attempted under any circumstances, unless a decision about re-challenge has been endorsed by the Sponsor.

Renal Stopping Criteria:

Special attention will be paid to:

1. Unexplained serum creatinine values greater than:
    a. two times the upper limit of the normal range at two consecutive test points following dosing; or
    b. one and one half (1.5) times the upper limit of the normal range at three consecutive test points following dosing or
2. Creatinine Clearance ≤ 30mL/min.

Creatinine clearance will be measured from serum creatinine based on the Cockcroft-Gault formula:

$$CrCl = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \quad (\times 0.85 \text{ for female patient})$$

If the study drug is thought to have caused the abnormalities, the Investigator may elect to discontinue study drug dosing. The cause should be thoroughly documented in the patient record. Such renal impairments should be reported as adverse events.

11.8 Pregnancy

If a patient becomes pregnant during the treatment period of the study or within 15 weeks after the last dose of study drug, the pregnancy must be reported.

If the pregnancy occurs during the treatment period, the study drug should be discontinued. Pregnancy itself is not an AE; however pregnancies must always be followed until completion or until pregnancy termination (i.e. induced abortion) and the outcome must be notified to the Sponsor or its representative.

The Investigator will be provided with a Pregnancy Report Form. This form must be completed and sent to the **PV Department of ICTA within 24 hours of awareness**. If the outcome of the pregnancy meets the criteria for a SAE (i.e. spontaneous miscarriage, congenital anomaly) the investigator must follow the procedures for SAEs reporting. Any complications occurring during pregnancy will be recorded as AEs and/or SAEs.

If the partner of a male patient becomes pregnant during the treatment period of the study or within the 15 weeks following the last dose of study drug, this should be reported to the investigator.

A specific informed consent will be provided to allow the collection of data concerning the follow-up and outcome of the pregnancy of the patient's partner.

Reporting and follow-up of the partner pregnancy will be done as mentioned above.

11.9 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) will formally review study safety data to ensure there is no avoidable increased risk for harm to patients. The DSMB will meet no less frequently than 3 times per year, with additional meetings at the discretion of the DSMB based on the review of ongoing data and observations. Analyses for the DSMB will be provided by the CRO mandated by Cerenis.

12 STATISTICS

12.1 Statistical Methods

Data will be analyzed by the mandated CRO. All cases will be checked for consistency and completeness by the Data Management Department of the mandated CRO.

Demographic and other baseline characteristics will be summarized across all randomized patients. Baseline is defined as the last observation for any given parameter prior to the first infusion of study drug. Comparability at baseline among treatment groups will be assessed using descriptive statistics without formal statistical tests.

The statistical techniques that are proposed in the sections below require certain assumptions. These assumptions will be checked for validity, and if they are not tenable, then appropriate statistical procedures will be utilized to complement the proposed procedures. Further detail on the statistical analysis is provided in the TANGO Statistical Analysis Plan (SAP) and decisions about analysis methods based on distribution assumptions will be documented in a review of the data before unblinding.

12.2 Efficacy Assessments

12.2.1 Primary Efficacy Analysis

The primary efficacy parameter of this study will be the change from baseline to 24 weeks in carotid MVWA in all randomised patients.

The primary efficacy endpoint, difference in the change from baseline in carotid artery Mean Vessel Wall Area (MVWA) at 24 weeks in patients treated with CER-001 compared to patients treated with placebo, will be analysed by an analysis of covariance (ANCOVA) model that includes treatment group and baseline MVWA as well as ABCA-1 or ApoA-1 genetic mutation as a covariate. Adjusted means for the change in MVWA in each treatment group and the difference between CER-01 and placebo will be provided, along with a 95% confidence interval.

Results (in terms of 95% confidence intervals for treatment effects) will also be presented for each of the ABCA-1 and ApoA-1 subgroups.

12.2.2 Secondary Efficacy Analysis

The secondary efficacy endpoints of this study will include the following:
Change from baseline MVWA by 3T-MRI:

- In the carotid artery at 8 and 48 weeks versus placebo
- In the femoral artery at 8, 24 and 48 weeks versus placebo

- Change from baseline in target (plaque) to background (blood) ratio based on standardised 18FDG uptake measured with 18FDG-PET/CT.

All the above secondary endpoints will be analysed using similar ANCOVA model as for the primary endpoint.

There is only one primary endpoint; no multiplicity adjustments will be made for the secondary endpoints.

12.2.3 Other Efficacy Analysis

The other efficacy endpoints of this study will include the following:
Change from baseline MVWA by 3T-MRI:

- In the carotid artery at 72 weeks
- In the femoral artery at 72 weeks

All the above endpoints will be analysed using similar ANCOVA model as for the primary endpoint.

12.2.4 Exploratory Efficacy Analysis

Change from baseline in carotid MVWA at six months will be examined in each genetic subset as a sensitivity analysis; the study is not powered to detect a difference between CER- 001 and placebo for individual genetic subgroups, this analysis is performed to assess whether trends in the subgroups are directionally consistent with the results of the total study population. The genetic subsets will also be examined for the other secondary endpoints listed above.

Other efficacy endpoints for the study will include the following and will be examined both for the full study population and for each genetic subset:

- The percent change in femoral artery MVWA versus placebo
- The percent change in maximum vessel wall thickness (MaxVWT) versus placebo
- The percent change in mean vessel wall thickness (MVWT) versus placebo
- The percent change in carotid mean vessel wall volume (MVWV) versus placebo
- The absolute change in carotid MVWV versus placebo
- The percent change in the mean of the carotid normalized wall index (NVWI) versus placebo
- The percent change in femoral artery MVWV versus placebo
- The absolute change in femoral MVWV versus placebo

These exploratory efficacy biomarkers will be summarized by treatment group using descriptive statistics (n, mean, standard deviation, median and range), or frequencies and percentages, as appropriate.

12.3 Safety Assessments

Safety will be assessed based on reporting of adverse events, physical examinations, clinical laboratory test results, vital sign measurements, and electrocardiogram (ECG) measures.

12.3.1 Safety and Tolerance Variables

Safety and tolerance variables will include:

- Incidence, severity and causality of AEs and particularly coronary events
- Change from baseline in physical examinations, clinical laboratory tests, vital signs and ECGs

12.3.2 Analysis of Safety and Tolerance Variables

Descriptive statistics will be provided for all safety parameters.

Adverse events will be coded by body system and preferred term based on the Med-DRA dictionary of standardized terminology. All AEs reported during the study will be listed, documenting course, severity, relationship to study drug and outcome. Adverse events will be tabulated by study treatment.

Summary tables will give the number and proportion of patients who experienced an AE, broken down by body system, preferred term and maximum severity. Related adverse events, defined as those adverse events that are possibly, probably or definitely related to study drug, will be summarized similarly.

Laboratory parameters, vital signs, physical exam results, and ECG findings will be summarized by treatment group and time point using descriptive statistics (n, mean, standard deviation, median and range), or frequencies and percentages, as appropriate. Results will be classified as normal or abnormal at screening and at on-treatment and follow-up visits. Shift tables of these values will be provided to summarize the change between screening and on-treatment / follow-up for each treatment group.

12.4 Sample Size Calculation

The assumptions upon which the power calculations are based are data from the 7 patients completing the CER-001-CLIN-007 SAMBA study, given the similarity of the genetic mutations. Those patients presented with a median value for MVWA of 25.0 mm2 and had a follow-up median value at 6 months of 21.8 mm2. The mean percent reduction is reported as 6.7%, standard deviation = 4.5%. These observed values would provide a conservative estimate of the effect of CER-001 in the more severe population for this FPHA study.

Using these results from SAMBA (i.e. an assumed standard deviation of 4.5%) and a 2:1 randomization scheme to maximize exposure to active drug, 16 completing patients in the CER-001 group and 8 in the placebo group (24 total completers for mITT) would yield 90% power to detect a difference from baseline versus placebo of 6.7%, using two-tailed testing with α=0.05. A total of

30 patients are planned to be randomized that would provide a buffer such that a 20% discontinuation rate would still allow the study to retain sufficient power for a supporting per protocol efficacy analysis (MVWA).

12.5 Populations for Analysis

The objectives of this study will be addressed primarily through the modified Intention-to-Treat (mITT) approach. In this approach all randomized patients with at least one valid, post randomization efficacy measurement, i.e., a follow up evaluation, will be included in the efficacy assessments, irrespective of their protocol adherence. Additionally, a per-protocol analysis will be performed which will only include patients who received all infusions of study drug (up to the time of each analysis), at the planned dosage and have no major protocol violations. Documentation of patients included / excluded from analysis populations will be completed before the study is unblinded.

For safety evaluations, all randomized patients who received at least one dose of study medication will be included.

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PART 2: ETHICS AND GENERAL STUDY ADMINISTRATION ETHICAL ASPECTS

14 ETHICAL CONSIDERATIONS

14.1 Institutional Review Board/Ethics Committee

This protocol and all appropriate amendments will be properly reviewed and approved by an Ethics Committee (IEC) or Institutional Review Board (IRB). Signed and dated notification of the IRB/IEC's approval must be made to the Sponsor and Investigator prior to study initiation.

14.2 Ethical Conduct of Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki amended, Fortaleza, Brazil, October 2013, (Appendix B) , GCPs (ICH E6) and in compliance with the standard operating procedures, local regulatory requirements and complying with the obligations and requirements of clinical Investigators and all other requirements listed in Code of Federal Regulations, FDA title 21 part 312 (21 CFR part 312).
Patient identity will be kept confidential, and to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient identity will remain confidential.

14.3 Patient Information and Consent

Informed consent will be obtained in accordance with ICH/GCP Guidelines and The Declaration of Helsinki and will be implemented before protocol specific procedures are carried out. The risks and benefits of participating in the study will be verbally explained to each potential patient prior to signing the consent form. Prior to the conduct of any screening tests or procedures, the patient must sign and date the written informed consent (which also defines the risks and benefits of participating in the study) in accordance with local regulatory and legal requirements. The Sponsor will provide a sample informed consent to the Investigators. The final form must be approved by the Sponsor/CRO and an IRB/IEC. It must contain all the elements in the sample form using language readily understood by the patients.

The date of receipt of written informed consent must be recorded in each patient's CRF and medical records. The signed consent form will be retained by the Investigator and a copy will be provided to each participant.

14.4 Protocol Adherence

The Investigators must read the protocol thoroughly and must follow the instructions exactly. Any protocol deviations will be documented and will be reviewed during the data review meeting.

Investigators must ensure that any amendment containing major modifications (particularly if it may involve an increased risk to the patients) is approved by the IRB/IEC before it is implemented.

15 CONFIDENTIALITY AND ARCHIVING

15.1 Personal data protection and Confidentiality

The investigator must assure that the personal data of patients, including their identity and all other personal medical information, will be kept confidential at any time.

Patient number and initials will identify the patients in the eCRF. On other documents or photographic materials (including the results of imaging) submitted to the sponsor, patients will not be identified by their names but by an identification code (e.g. initials and patient number).

By signing this protocol, the investigator undertakes that the protocol and all attached information are and will remain confidential. The investigator agrees that after providing the protocol and all information necessary for the personnel involved, he remains responsible for their total confidentiality. Such obligation is detailed in the confidentiality agreement signed by the investigator before the initiation of the study.

The investigator agrees that, subject to local regulations and ethical considerations, a sponsor representative or any regulatory agency may consult directly and/or copy study documents in order to verify a case report, provided that the subject's identity remains anonymous.

The investigator undertakes to treat all subjects data used or disclosed in connection with the conduct of study in compliance with European and local applicable laws relating to data protection.

The investigator will be responsible for keeping a list of all enrolled patients including patient numbers, full names and date of birth.

15.2 Study documentation keeping

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. The study documents, including patient CRFs, should be classified in the investigator's file.

The investigator's file will contain the protocol/amendments, independent Ethics Committee and Health Authorities with correspondence, sample informed consent, IMP records, staff curriculum vitae and authorization forms, correspondence, etc.

The investigator must keep the Study File until the Sponsor authorization of destruction and by default during at least 15 years after completion or discontinuation of the study.
Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

16 DATA HANDLING AND RECORD KEEPING

16.1 Data Collection

An electronic data capture system will be used in the clinical study. The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor/CRO's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Any source data that is not captured electronically will be captured on paper source documents. The appropriate data from these paper source documents will then be manually entered into an electronic data capture system according to the data entry guidelines.

16.2 Data Corrections

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. Any missing, impossible or inconsistent data will be referred back to the Investigator. This information will be provided to the respective study sites by means of electronic or manual queries, using a data query form and be documented for each individual patient before clean file status is declared.

Any changes made to the data after approval by the site monitor will be discussed with and approved by the Investigator.

16.3 Source Documentation

The Investigator will keep accurate separate records (other than the CRFs) of all patients' visits, being sure to include all pertinent study related information. A statement will be made in the patient chart indicating that the patients have been enrolled in Protocol CER-001-CLIN-009 and the visit dates. Thoroughly document all side effects and AEs in the patient chart. Include results of any diagnostic tests conducted during the study in the source documentation. Record any telephone conversations with the patient and/or Sponsor concerning the study.

16.4 Monitoring, Quality Control and Quality Assurance

The Sponsor/CRO will be responsible for monitoring the study, data entry and data management. If designated by the Sponsor, the CRO will also perform quality control of the study and database.

The CRAs will be trained prior to study initiation. This training will include an overview of the study disease and study drug background. Specific monitoring guidelines and procedures will be reviewed.

A pre-study/initiation visit will be conducted with all Principal Investigators, Study Coordinators, and Study Pharmacists. During this meeting, an extensive review and discussion of the protocol and associated procedures will be conducted, including the procedures for study drug preparation and dosing. The conduct of the study will be closely monitored by representatives of CRO and the Sponsor following GCP guidelines. The reports of these verifications will also be archived with the study report.

In addition, inspections or on-site audits may be carried out by local authorities or by CRO and the Sponsor's independent Quality Assurance Department or designee. The Investigators will allow CRO and the Sponsor's representatives and any regulatory agency to examine all study records, CRFs, corresponding patient medical records, clinical drug dispensing records and drug storage area, and any other documents considered source documentation. The Investigators also agree to assist the representative, if required.

16.5 Record Retention

Maintain all CRFs and pertinent data, correspondence, original or amended protocol, all reports and all other material relating to the study securely in the Investigator's files for one of the following two periods:

- a period of at least two years following the date on which the study drug is approved by FDA for marketing for the purposes that were the indication studied; or
- If no application is to be filed or if the application is not approved for the indication studied, a period of at least two years after the date on which the entire investigation (all clinical studies) is terminated and the FDA is notified.

In any event, do not destroy study documentation without the express written permission of Cerenis™ Therapeutics. If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor and IRB/IEC must be notified in writing of the name and address of the new custodian.

17 FINANCING AND INSURANCE

The contractual details between the Investigator and the Sponsor are contained in a separate agreement. During the study, the Sponsor will hold Clinical Trial Insurance with coverage commensurate to the risks associated with the study.

18 PUBLICATION OF STUDY RESULTS

The TANGO Steering Committee is responsible for preparing the manuscripts and presentations and will publish the results of this study after providing a draft manuscript to the Sponsor for review and comment at least 45 days prior to submission.

19 CLINICAL STUDY REPORT (CSR)

A clinical study report will be written and distributed to Health Authorities as required by applicable regulatory requirements.

The sponsor will designate a principal coordinating investigator (who will sign the final study report) based on their contribution to the conduct of the study, and/or their expertise employed in the interpretation of the overall study results.

20 OTHER INFORMATION

This study will be registered on the clinicaltrials.gov website.

APPENDIX A: Schedule of Assessments in double-blind treatment phase

	Screening	Randomization Baseline	Period 1 Induction Infusion every week				Period 2 Maintenance Infusion every two weeks				Period 3 Extension				Period 3 Extension		Final safety
	V1	V2 W0	V3 to V5 W1 to W3	V6 W4	V7 to V9 W5 to W7	V10 W8	V11 to V13 W10 to W14	V14 W16	V15 to V17 W18 to W22	V18 W24	V19 to V21 W26 to W30	V22 W32	V23 to V25 W34 to W38	V26 W40	V27 to V29 W42 to W46	V30 W48	V31 W52
Informed consent	X																
Selection criteria	X																
Demography	X																
Medical history (smoking status)	X																
Counseling on heart healthy diet and lifestyle	X																
Vital signs	X	X		X		X		X		X		X		X		X	X
Blood pressure & heart rate assessment *BP and HR should be measured pre-infusion and post-infusion	X	X		X*		X*		X*		X*		X*		X*		X*	X
Heigh	X																
Weigh	X	X		X		X		X		X		X		X		X	
Physical exam	X	X		X		X		X		X		X		X		X	X
12-lead ECG	X	X		X		X		X		X		X		X		X	X
Adverse events[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH[2]	X																
Serum Pregnancy Test	X																
Urinary Pregnancy Test		X		X		X		X		X		X		X		X	
Hematology/coagulation[3]	X	X		X		X		X		X		X		X		X	X
Serum chemistry[4]	X	X		X		X		X		X		X		X		X	X
Urinalysis[5]	X	X		X		X		X		X		X		X		X	X
Markers of inflammation, oxidation and CV risk[6]	X	X		X		X				X						X	
Anti-ApoA-1 antibody	X					X				X						X	
Fasting plasma glucose[7]	X	X		X		X		X		X		X		X		X	
HBA1c	X	X															
Biomarkers sample		X								X							
Lipid & Lipoprotein profile[8] (from fasting samples)	X	X				X				X						X	
Cholesterol Efflux[9]	X	X				X				X						X	
Genotyping[10]	X																
Study drug infusion[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics[12] (2 hours after starting the infusion)		X								X							
3TMRI (MVWA)		X				X				X						X	
18F-FDG-PET/CT (if site equipped to do it)		X								X							

1. AEs and SAEs (related or not related) to be recorded at each visit until the final study evaluation. After the end of the study, only the SAEs likely to be related to the study medication or study procedures must be notified.
2. FSH in women whose last menstrual period was between 6 and 12 months before screening
3. White blood count, red blood count, hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, differential
4. Glucose, Blood Urea Nitrogen (BUN), Creatinine, Total Bilirubin, Indirect Bilirubin, Aspartame Aminotransferase 5AST/SGOT), Alanine Aminotransferase (ALT/SGPT), Alkaline Phosphatase, Total Protein, Albumin, Lactate Dehydrogenas (LDH), Creatinine Kinase (CK), Sodium, Potassium, Chloride, Carbon dioxide, Uric Acid, Calcium, Phosphorous
5. Microalbuminuria, Specific Gravity, pH, Glucose, Total Protein, Ketones, Total Bilirubin, WBC, RBC, Casts.

6. Markers of inflammation, oxidation and CV risk and other markers (hsCRP, TNFα, IL6, sVCAM, PON-1, MMP-9, Oxysterols (FACS Analysis), sMCP1, ABCA1 mRNA, protein levels (Monocytes))

7. Patient must have fasted (ie not to take any food or liquids other than water) for 8 hours prior to blood sampling.

8. Patient must have fasted (ie not to take any food or liquids other than water) for 8 hours prior to blood sampling. Total cholesterol, unesterified cholesterol, esterified cholesterol, apolipoprotein A-1, apolipoprotein B, other apolipoprotein, Apolipoprotein profil, triglycerides, HDL-C, LDL-C + subfractions. HDL-C particles assessment including pre- analyzed by NMR and **2D-gel**. Additionally, oxPhopholipids (OxPL) will be assessed.

9. At infusion visits, samples should be drawn 2 hours after the start of the infusion.

10. Mandatory assessment of the genetic mutation at screening. A DNA sample will be taken ONLY for determination of the presence of HDL gene mutations specifically for ABCA1 and ApoA-1 mutation(s) in case the patient was to satisfy all other selection criteria and would not have a confirmed related genetic mutation. Genotyping will be performed centrally.

11. Visits may be scheduled +/- 2days from target weekly or biweekly date.

12. PK assessment including 2D-gel.

13. 3T-MRI and 18FDG-PET/CT should be collected with a window of +/- 7 days around the strict date.

14. Safety follow-up visit will be performed 4 weeks +/- 7 days after the last dose of study medication for all patients.

APPENDIX B: Schedule of Assessments in open-labeled treatment phase

	V31 to V41 W50 to W70	**V42** W72	**V43 FU** W76
Informed Consent	X		
Selection criteria (Inclusion/Exclusion)			
Medical history			
Demography			
12-Lead ECG			
Height			
Weight			
Pregnancy Test			
Physical Exam			
Vital Signs			
Blood Pressure (BP) & Heart Rate (HR) assessment			
Hematology/coagulation			
Serum Chemistry			
Urinalysis			
Adverse Events	X	X	X
Previous and concomitant medications	X	X	X
FSH			
Counseling on heart healthy diet and lifestyle			
Genotyping			
Markers of inflammation, oxidation and CV risk			
Biomarkers sample			
HBA1c			
Fasting blood glucose			
Lipid & Lipoprotein Profile			
Anti-ApoA1 antibody			
Creatinine and/or BUN testing to determine GFR			
Cellular Cholesterol Efflux			
Study drug infusion	X	X	
Pharmacokinetics (PK)			
3TMRI (MVWA)		X	
^{18}FDG-PET/CT			

APPENDIX C: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION - DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and

therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or

compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made

the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.