CARAT

CER-001 ATHEROSCLEROSIS REGRESSION ACS TRIAL

A PHASE II MULTI-CENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-FOCUSING TRIAL OF CER-001 IN SUBJECTS WITH ACUTE CORONARY SYNDROME

CLINICAL PHASE: II
EudraCT number 2015-001381-26

PROTOCOL NUMBER: CER-001-CLIN-010

Version: V1.1 23rd March 2015

Revision History: V1 16th February 2015

Sponsor:

CERENIS THERAPEUTICS SA
265 Rue de la Découverte
BAT.A
31670 LABEGE
France

Academic Leadership:

Managed by the South Australian Health and Medical Research Institute in conjunction with Regional Operational Academic Research Organizations. The CARAT Executive Committee, which is involved in the oversight of the trial, includes members who are independent academics.

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SYNOPSIS

TITLE OF STUDY: CARAT
CER-001 Atherosclerosis Regression ACS Trial
A Phase II Multi Center, Double Blind, Placebo-Controlled, Dose-Focusing Trial Of CER-001 InSubjects With Acute Coronary Syndrome (ACS).

INVESTIGATIVE SITES:
Approximately 40 sites in Australia, USA, Hungary, and The Netherlands.

ANTICIPATED STUDY DURATION:
Anticipated Start Date for Study Enrollment: July 2015
Anticipated Completion Date for Study Enrollment: April 2016
Anticipated Date for Last Subject’s Last Visit: July 2016

OBJECTIVE:
To assess the impact of ten intravenous infusions of 3 mg/kg CER-001 vs. placebo, given at weekly intervals, on atherosclerotic plaque volume as measured by coronary IVUS, when administered to subjects presenting with Acute Coronary Syndrome (ACS) with significant plaque volume.

METHODOLOGY:
Subjects with an ACS event undergoing a clinically indicated coronary angiography, having signed informed consent will be eligible.

Subjects will be required to have at least one epicardial coronary artery suitable for IVUS imaging. A suitable target artery for IVUS imaging will be determined at baseline as having stenosis of up to 50% and meeting all angiographic inclusion criteria. Subjects having met all eligibility criteria including acceptance of the baseline IVUS by the IVUS Core Laboratory for overall quality and ≥30% PAV in the most proximal 10 millimeters, will be randomized to receive an intravenous infusion of CER-001 (3 mg/kg) or placebo given over 30 minutes. Randomization and Infusion 1 will occur within 14 days of event presentation. Randomized subjects will then return at 7 day intervals (window of +/- 2 days) for nine additional infusions. End-of-treatment labs will be drawn 7 days (window of +/- 2 days) after the last infusion. A follow-up IVUS will be conducted at 14 days (window of +/- 7 days) after the last infusion. The total study duration from randomization to follow up IVUS for a completed study can range from approximately 9 to 12 weeks. A telephone follow-up will be done one month (30 days) after the final dose of study medication to collect information on any adverse events which may occur after the follow-up IVUS visit.
NUMBER OF SUBJECTS:
292 subjects treated in order to achieve 248 completed subjects total, or 146 randomized per treatment group (3 mg/kg CER-001 or Placebo).

Randomized subjects will have ten weekly infusions, followed by an end-of-study lab visit and a follow-up IVUS procedure. The anticipated length of study for an individual subject is planned to be 84 days, but may range from 53 to 103 days depending on actual visit dates.
PRODUCT INFORMATION

TREATMENT GROUPS:
CER-001 is a negatively charged apoA-I-containing lipoprotein/phospholipid complex mimicking natural HDL.

COMPARATOR PRODUCT:
Normal saline will be used as the placebo.

ASSESSMENTS:
- IVUS
- Adverse events (AEs)
- Clinical laboratory measurements
- Pharmacokinetic and pharmacodynamic parameters
- Electrocardiograms (ECGs)
- Physical Exams
- Vital Signs

SAMPLE SIZE CALCULATION:
Sample size computation is based on the assumption that the study has 86% power to demonstrate a difference in the change in PAV between the treatment groups of 1.0% with a standard deviation of 2.6%.

This requires 248 subjects with evaluable IVUS imaging at baseline and follow up. To account for an attrition rate of 15%, 146 subjects per group will be randomized per treatment group so that a total of 292 subjects will be randomized in this study.

PRIMARY EFFICACY PARAMETER:
The primary efficacy parameter for this study is the nominal change from baseline to follow-up in the Percent Atheroma Volume (PAV) in the target coronary artery assessed by IVUS. The primary endpoint will be a comparison of the primary efficacy parameter between randomized treatment groups (Placebo vs. CER-001 3 mg/kg) using an analysis of covariance (ANCOVA) with adjustment for baseline PAV. The adjusted mean endpoint in each treatment group and the difference in means (95% confidence interval) will be presented. Statistical significance will be assessed at the alpha=0.05 level. The ANCOVA model will be replaced with non-parametric testing if the normality assumption is violated.
SECONDARY EFFICACY PARAMETERS:
Secondary atherosclerosis efficacy parameters will include the (i) nominal change from baseline to follow-up in normalized Total Atheroma Volume (TAV) and (ii) nominal change in TAV in the 10-mm sub segment of the coronary artery with the largest plaque volume at baseline (the most diseased segment).

EXPLORATORY EFFICACY PARAMETERS:
1. Pre- to post-dose changes in lipoprotein profiles by HPLC at the first and last doses.
2. Pre- to post-dose changes in apoA-I levels at the first and last doses.
3. Pre- to post-dose changes in cellular cholesterol efflux capacity at the first and last doses.
4. Pre-dose lipid profiles, including low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol (TC), unesterified cholesterol (UC), triglycerides (TG), phospholipids (PL), apolipoprotein A-I (apoA-I) and apolipoprotein B (apoB), will be determined periodically throughout the study (see Appendix A).
5. Baseline to follow up changes in any plaque characteristic measurements taken during the IVUS procedure.
6. Episodes of all death (to determine whether cardiovascular death occurred), non-fatal myocardial infarction, resuscitated cardiac arrest, non-fatal stroke, fatal stroke, coronary revascularization procedures [percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)], hospitalization for unstable angina, urgent visit or hospitalization for congestive heart failure (CHF), any admission for a procedure for the treatment of PVD (including cerebrovascular procedures) and urgent readmission with chest pain (to determine whether a diagnosis of MI or unstable angina should be made) will be recorded by the Investigator using electronic Case Report Forms (eCRFs). The events will be reviewed and adjudicated by the Clinical Endpoint Committee according to established definitions. This study is not powered for MACE endpoints.
SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

INCLUSION CRITERIA

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

1. Subjects must provide informed consent, as approved by the IRB/EC, prior to performance of any screening procedures
2. Male or female at least 18 years of age
3. Subject of non child-bearing potential;
   a) Greater than 12 months since last menstrual period; and/or Surgically sterilized and agree to use barrier method of birth control for the entire study; and/or
   b) On hormonal therapy (including implants, injections, combined oral contraceptives and IUDs) and agree to use a barrier method of birth control for the entire study; and/or
   c) Agree to use a double barrier method of birth control defined as condom in combination with diaphragm, contraceptive sponge, spermicidal foam or cervical cap.
4. Subjects who undergo coronary angiography within 7 days of presentation with ACS:

   ACS Criteria Myocardial Infarction
   a) Cardiac biomarkers (troponin I or T, CKMB mass, or CK-MB activity) with at least one determination > 99th percentile or above the local laboratory upper reference limit
   AND one of the following:
   b) Chest pain or ischemic symptoms at rest >10 minutes within prior 24 hours
   c) New ECG changes of acute ischemia (LBBB, ST elevations, or ST depressions)
   d) New pathologic Q-waves or R/S >1 in V1- V2
   e) Regional myocardial scar or ischemia by nuclear, magnetic resonance, echocardiographic, or angiographic imaging

   OR Biomarker-Negative ACS (Unstable Angina)
   a) No elevation of cardiac biomarkers
   b) Chest pain or ischemic symptoms at rest >10 minutes
   c) Prompting Hospitalization or chest pain observation unit within 24 hours of symptoms
   AND one of the following:
   d) New or worsening ECG changes (transient ST elevation, ST depression, or T inversion)
   e) Definite myocardial ischemia on nuclear or echocardiographic imaging
   f) Angiographic stenosis >70% or thrombus in epicardial coronary artery or bypass graft and/or performance of PCI
5. Baseline Coronary angiogram must meet all the following criteria for IVUS interrogation of Target Artery;

Target Artery:

a) Must be accessible to the IVUS catheter
b) Must have a stenotic area of ≤50% in lumen diameter by angiographic visual estimation within the length of the native coronary artery for imaging by IVUS
c) The target artery may not be a bypass graft
d) The target artery may not be the culprit vessel for a previous MI

Target Artery May Have:

a) A lesion up to 60% stenosis, distal to the target segment, provided that this area is not anticipated to be a target for PCI or CABG during the course of the study
b) A single branch of the target artery may have a narrowing ≤70% by visual estimation, provided that the branch is not a target for PCI or CABG during the course of the study

6. Subject is able to be randomized within 14 days of ACS event presentation

7. Baseline IVUS interrogation determined to be of acceptable quality with PAV ≥ 30% in the proximal 10 mm at review by the Imaging Core Lab

8. Subject must be willing to participate in the study and comply with all protocol requirements, including willingness to:

a) Return to the clinic weekly for a total of ten IV infusions of study drug.
b) Return to the clinic for follow up visits.
c) Return to the clinic at the end of the study for follow up IVUS procedure.

EXCLUSION CRITERIA

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

1. Baseline IVUS not completed due to non-qualifying coronary angiogram as demonstrated by:
   a) Greater than 50% reduction in lumen of the left main coronary artery by visual estimation
   b) Extensive coronary artery disease with no target vessel for IVUS interrogation
   c) Angiographically normal coronary arteries

2. Baseline IVUS interrogation determined to be unacceptable by the Imaging Core Lab

3. Subjects with uncontrolled diabetes defined as HbA1c > 10% at Screening

4. Subjects with triglycerides >500 mg/dL at Screening

5. Subjects with coronary artery bypass graft (CABG) surgery in previous 6 weeks or in whom CABG is planned
6. Myocardial infarction in the target coronary artery for IVUS between the initial IVUS examination and randomization.

7. Subjects who have symptomatic congestive heart failure (CHF) (New York Heart Association [NYHA] Class III or IV) at baseline.

8. Subjects with a known ejection fraction <35% (investigations to document EF not required)

9. Subjects with clinically significant valvular heart disease likely to require surgical repair or replacement during the treatment period of the study.

10. Subject is hemodynamically or clinically unstable in the opinion of the Investigator.

11. Subject has uncontrolled hypertension (e.g., sitting systolic BP > 180 mm Hg on antihypertensive therapy) at time of randomization.

12. Subject has known major hematologic, hepatic (liver enzymes greater than twice the upper limits of normal for the performing laboratory), metabolic, gastrointestinal or endocrine dysfunction in the judgment of the Investigator.

13. Subject has known renal dysfunction \( \text{CrCl} \leq 30 \text{ ml/min} \)

14. Any clinically significant medical condition or presence of any laboratory abnormality performed prior to randomization that is considered by the investigator to be clinically important and could interfere with the conduct of the study.

15. Subject is likely to be unreliable as a study participant based on the Investigator's (or designee's) knowledge of the subject (e.g., alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis).

16. Subject has participated in any investigational drug or interventional device study within 30 days prior to randomization, or expects to participate in any other investigational drug or interventional device study during his/her planned participation in this study.

17. Subject has previously participated in this study or another study involving CER 001.

**SUBJECT RESTRICTIONS DURING THE STUDY**

There are no subject restrictions other than those outlined in the Inclusion/Exclusion criteria above.

**SAFETY AND TOLERANCE**

- Incidence and severity of Adverse Events (AEs) from routine monitoring
- Incidence of abnormalities and changes from baseline in clinical laboratory parameters from testing of blood and urine
- Incidence of changes from baseline vital sign values
- Incidence of changes from baseline physical examinations
- Incidence of changes from baseline ECG parameters
SAFETY EVALUATION
All subjects who receive study medication and have a subsequent safety evaluation will be included in the safety analyses. 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. AEs of special interest will include infusion or allergic reactions and liver enzyme elevations. Case summaries will be provided for these cases, as well as AEs leading to withdrawal, serious AEs and any events not considered AEs because they are determined to be MACE.

Adverse events will also be tabulated by study treatment. Summary tables will give the number and proportion of subjects 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 SCR and at the FIVUS visits. Shift tables of these values will be provided to summarize the change between SCR and the FIVUS visit for each treatment group.

ASSESSMENT OF SAFETY
Periodic safety review will be performed during the on-treatment period by a data 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 subject monitoring or treatment plans during the remainder of the on-treatment period.
## METHODS AND TIMING FOR ASSESSING SAFETY PARAMETERS

### CLINICAL LABORATORY TESTS

Clinical laboratory safety testing during the screening and treatment periods will be performed by a central laboratory. Collection kits, shipment instructions, and a detailed 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. A serum pregnancy test will be done at the Screening and Final IVUS visits on pre and perimenopausal females (less than 12 months since last menstrual period).

In the case of an adverse event of special interest (allergic/infusion reaction or LFT 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. A Medical hotline will be available 24 hours for consultation.

### ADVERSE EVENT REPORTING

#### MAJOR ADVERSE CARDIOVASCULAR EVENTS

Suspected major adverse cardiovascular events (MACE) will be collected by the Investigator and adjudicated by the Clinical Endpoint Committee (CEC) related to the following conditions:

1. Cardiovascular death
2. Non-fatal myocardial infarction
3. Resuscitated cardiac arrest
4. Coronary revascularization procedures (PCI, CABG)
5. Hospitalization for unstable angina
6. CHF event (urgent visit and hospitalization)
7. Fatal and non-fatal strokes
8. Any admission for a procedure for the treatment of PVD (including cerebrovascular procedures)

Positively adjudicated events will not be reported as AEs in the study; negatively adjudicated events will be reported as AEs and/or SAEs as appropriate for the circumstances. This study is not powered for MACE endpoints.

### LIST OF APPENDICES

Appendix A: Study Procedures Flow Sheet
PROTOCOL APPROVED BY SPONSOR'S REPRESENTATIVES

Constance H. Keyserling, M.S.
Senior Vice President, Clinical Development and Operations
Cerenis Therapeutics
265 Rue de la Decouverte
BAT.A
31670 LABEGE
France

Signature: Constance H. Keyserling  Date: 24 mar 2015

Renée Benghozi
Chief Medical Officer
Cerenis Therapeutics
265 Rue de la Decouverte
BAT.A
31670 LABEGE
France

Signature:  Date: 24/03/2015
PROTOCOL APPROVED BY PRINCIPAL INVESTIGATOR

Site Number CER-001-CLIN-010-_______

Investigator Name:
_________________________________________________________

Investigator Address:
_________________________________________________________
_________________________________________________________

Telephone: _______________________________________________
Fax/Email: ________________________________________________

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practices (cGCPs; ICH E6), the Declaration of Helsinki and complying with the obligations and requirements of clinical Investigators and all other requirements listed in §21 CFR part 312.
I agree to inform all subjects 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 cGCPs and regulatory authority requirements.

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

Investigator Signature: ___________________________ Date: ____________
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1 STUDY RESPONSIBILITIES

Sponsor
Cerenis Therapeutics SA
265 Rue de la Decouverte
BAT.A
31670 Labège
FRANCE

IVUS Core Laboratory
The South Australian Health and Medical Research Institute (SAHMRI)
North Terrace, Adelaide
South Australia
AUSTRALIA 5000

Academic Research Organisation
The South Australian Health and Medical Research Institute (SAHMRI)
North Terrace, Adelaide
South Australia
AUSTRALIA 5000

Medical Monitor
The South Australian Health and Medical Research Institute (SAHMRI)
North Terrace, Adelaide
South Australia
AUSTRALIA 5000

Central Safety Laboratory (CEC)
C5 Research, Heart and Vascular Institute
Cleveland Clinic
9500 Euclid Ave
Cleveland, Ohio 44195
USA
1 STUDY RESPONSIBILITIES cont.

Clinical Trial Material Labelling and Packaging

Catalent Pharma Solutions
10381 Decatur Road
Philadelphia, PA 19114
USA

Clinical Trial Material Distribution

Catalent Pharma Solutions
3031 Red Lion Road
Philadelphia, PA 19114
USA
# 2 LIST OF ABBREVIATIONS

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<tbody>
<tr>
<td>ACS</td>
<td>Acute Coronary Syndrome</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
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<tr>
<td>ARO</td>
<td>Academic Research Organisation</td>
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<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
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<tr>
<td>CER-001</td>
<td>Experimental compound under study</td>
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<td>CK-MB</td>
<td>creatinine kinase – MB fraction</td>
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<td>Blood Pressure</td>
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<td>Case Report Form</td>
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<td>HDL/LDL RATIO</td>
<td>High density lipoprotein/low density lipoprotein ratio</td>
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<td>High density lipoprotein cholesterol</td>
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<td>Head, Ears, Eyes, Nose, Throat</td>
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<td>HPLC</td>
<td>High-Pressure Liquid Chromatography</td>
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<tr>
<td>HR</td>
<td>Heart Rate</td>
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<td>ICH</td>
<td>International Conference on Harmonization</td>
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<td>Lactate dehydrogenase</td>
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<td>Low density lipoprotein</td>
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<tr>
<td>LDL-C</td>
<td>Low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>MACE</td>
<td>Major adverse cardiovascular event</td>
</tr>
<tr>
<td>Med-DRA</td>
<td>Medical dictionary for regulatory activities</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>mITT</td>
<td>modified Intent to Treat</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>PAV</td>
<td>Percent atheroma volume</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>PET-CT</td>
<td>Positron emission tomography–computed tomography</td>
</tr>
<tr>
<td>PL</td>
<td>Phospholipid</td>
</tr>
<tr>
<td>POPC</td>
<td>Palmitoyl-oleoyl-phosphatidyl-choline</td>
</tr>
<tr>
<td>PVD</td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cells</td>
</tr>
<tr>
<td>RINF1</td>
<td>Randomization and First Infusion Visit</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory Rate</td>
</tr>
<tr>
<td>SBPC</td>
<td>Soybean phosphatidyl-choline</td>
</tr>
<tr>
<td>SCR</td>
<td>Screening Visit</td>
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<tr>
<td>SGPT (ALT)</td>
<td>Serum glutamic-pyruvic transaminase/Alanine aminotransferase</td>
</tr>
<tr>
<td>SGOT (AST)</td>
<td>Serum glutamic-oxaloacetic transaminase/Aspartate amino transferase</td>
</tr>
<tr>
<td>SMFU</td>
<td>Safety Monitoring Follow Up</td>
</tr>
<tr>
<td>T2DM</td>
<td>Type 2 Diabetes Mellitus</td>
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<tr>
<td>TAV</td>
<td>Total atheroma volume</td>
</tr>
<tr>
<td>TFE</td>
<td>Time to first event</td>
</tr>
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<td>UAP</td>
<td>Unstable angina pectoris</td>
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<tr>
<td>UC</td>
<td>Unesterified cholesterol</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
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</table>
3 BACKGROUND

3.1 Investigational Product

Cerenis Therapeutics has developed CER-001, a negatively charged lipoprotein complex mimicking natural, nascent discoidal pre-high density lipoprotein (HDL), consisting of a combination of two naturally occurring phospholipids and recombinant human apolipoproteinA-I (apoA-I). The apoA-I 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-I protein component of the complex. CER-001 is intended for the treatment of complications due to atherosclerotic diseases.

3.2 Coronary Heart Disease: An Overview

Cardiovascular disease (CVD) remains the most important healthcare issue in the developed world and is rapidly becoming so in large parts of the developing world. The following facts from the American Heart Association (AHA) Heart Disease and Stroke Statistics from 2013 illustrate the magnitude of the problem in the US. Coronary heart disease alone caused ≈1 of every 6 deaths in the United States in 2009. In 2009, 386 324 Americans died of coronary heart disease. Each year, an estimated ≈635 000 Americans have a new coronary attack (defined as first hospitalized myocardial infarction or coronary heart disease death) and ≈280 000 have a recurrent attack. It is estimated that an additional 150 000 silent first myocardial infarctions occur each year. Approximately every 34 seconds,1 American has a coronary event, and approximately every 1 minute, an American will die of one. Each year, ≈795 000 people continue to experience a new or recurrent stroke (ischemic or hemorrhagic). Approximately 610 000 of these are first attacks, and 185 000 are recurrent attacks. In 2009, stroke caused ≈1 of every 19 deaths in the United States. On average, every 40 seconds, someone in the United States has a stroke and dies of one approximately every 4 minutes.

One in three individuals in the US has some form of cardiovascular disease. The aging of the population will undoubtedly result in an increased incidence of coronary artery disease, heart failure, and stroke. There has been an explosive increase in the prevalence of obesity and type 2 diabetes and their related complications (hypertension, hyperlipidemia, and atherosclerotic vascular disease) will also increase.
Cardiovascular disease claims more lives each year than the next 5 leading causes of death combined. The prevalence of cardiovascular disease in the US in 2010 was 35.3%. Mortality data show that CVD as the listed underlying cause of death (including congenital cardiovascular defects) accounted for 32.3% (787,931) of all 2,437,163 deaths in 2009, or ≈1 of every 3 deaths in the United States. Since 1900, cardiovascular disease has been the No. 1 killer in the United States every year but 1918.

2012 European cardiovascular disease statistics show that cardiovascular disease causes over 4 million deaths and 1.9 deaths in the European Union. CVD causes 47% of all deaths in Europe and 40% in the EU. It remains the leading cause of death in women in Europe and is the main cause of death in men in all but 6 countries. Death rates from CHD are generally higher in Central and Eastern Europe than in Northern, Southern and Western Europe.

There is a general trend with CVD mortality now falling in most European countries, including Central and Eastern European countries which saw large increases until the beginning of the 21st century, although death rates from stroke are many times higher in Central and Eastern Europe than in Northern, Southern and Western Europe.

In Australia, cardiovascular disease is the leading cause of death, with 43,946 deaths attributed to CVD in 2012. CVD kills one Australian every 12 minutes. It remains one of Australia’s largest health problems and is one of the biggest burdens on the economy. In 2010, high total cholesterol was the second greatest attributor to the total burden of heart disease, accounting for more than a third (36.3%) of the total burden. In 2011/12, 5.6 million people aged 18 and older had high total cholesterol. Overall, 33 per cent of Australians had high total cholesterol.

Despite the availability of several classes of very effective drugs, dyslipidemia and risk factor control are poorly served and there remains a large unmet medical need for new, effective and well tolerated therapies. There are a number of therapies given on a chronic basis to reduce long term risk, such as statins, fibrates, niacin, omega-3 fatty acids, resins, cholesterol absorption inhibitors and antiplatelet or anticoagulant drugs, but subjects are at the highest risk immediately after an acute event. There is a high need for acute therapies which can be given at, or near, the time of an event, that will lead to rapid pacification of unstable plaque.

3.3 Non-Clinical Findings for CER-001

CER-001, a recombinant human apoA-I/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-I 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.

3.4 Clinical Findings for CER-001

A Phase I single dose tolerance study has been completed in 32 subjects. 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 subjects, 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-I developed following single doses.

One Phase II pilot study called EXPRESS, a small 12-subject study in Heterozygous Familial Hypercholesterolemia to assess MRI and IVUS imaging endpoints, has been completed. The subjects enrolled in the study were not representative of the typical high plaque burden/high risk heterozygous FH subject with clinically active atherosclerosis; mean baseline 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 subjects who contributed evaluable data due to measurement difficulties (n=9) and the subsequent methodological concerns, no meaningful conclusions can be drawn regarding the effects of CER-001 on atherosclerotic plaque volume in subjects 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 3TMRI. Intravenous infusions of CER-001 administered at a weekly dose of 8 mg/kg for six weeks were well tolerated in these subjects with heterozygous FH.

A second Phase II study called CHI-SQUARE, in subjects with Acute Coronary Syndrome has also been completed. It was an ascending dose, placebo-controlled, double-blind, dose-response study that enrolled 507 subjects (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 as measured by IVUS for the 12 mg/kg CER-001 treated subjects compared to the placebo subjects. Methodologic 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. These results warrant further studies to be conducted in this indication, with particular focus on the 3 mg/kg dose.

![Figure 1. Change in IVUS parameters by treatment group and analysis population](image)

(Change from Baseline PAV: mITT, mPP, PPP; Change from Baseline TAV: mITT, mPP, PPP)

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. Subjects treated with CER-001 had more serious adverse events and withdrew from study medication due to adverse events more often than placebo-treated subjects. The increased frequency of events was mainly in the 6 and 12 mg/kg CER-001-treated subjects. When these trends were analyzed, it appears that the differences are mainly due to the occurrence of infusion reactions in CER-001-treated subjects (see Sections 3.6 Risk Benefit Statement and 10.4 Expected Side Effects).

A Phase II study in Homozygous Familial Hypercholesterolemia (HoFH) called MODE has also been completed. It was an open-label, single arm active treatment study that enrolled 23 subjects. 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 mm³ at baseline to 16.75 mm³ at Month 6 (2.53%; p=0.0124) in the mITT population (n=18 subjects with baseline and follow-up 3TMRI 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 subjects. There was only one report of a treatment-related SAE, an urticarial reaction which resolved rapidly with treatment.

A Phase II study in Familial HDL-c Deficiency also referred to as Familial Primary Hypoalphalipoproteinemia (FPHA), called SAMBA, has also been completed. It was an open-label, single arm active treatment study that enrolled nine subjects. The primary study objective was to determine whether the pharmacokinetic and pharmacodynamics behaviour of CER-001 was the same in subjects 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 subjects who had adequate collection of follow-up data have recently been published. They are encouraging and demonstrate that CER-001 increases elimination of cholesterol from the body and regresses carotid artery inflammation and atherosclerosis⁴. No SAEs were reported nor did any subjects discontinue therapy due to an AE. Blood chemistry and hematology findings were unremarkable for this subject population. Additional studies are planned in this indication.


3.5 Description and Mechanism of Action of CER-001

CER-001 is a complex comprised of recombinant human apoA-I 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.

3.6 Risk Benefit Statement

Subjects enrolled in this study will have a second coronary catheterization performed approximately 12 weeks following their initial catheterization and will therefore be exposed to the risks associated with the second catheterization procedure. Cardiac catheterization is a common medical procedure that rarely causes serious problems, however, complications can include:

- Bleeding, infection, and pain where the catheter was inserted.
- Damage to blood vessels. Rarely, the catheter may scrape or poke a hole in a blood vessel as it's threaded to the heart.
- An allergic reaction to the dye used.

Other, less common complications of the procedure include:

- Arrhythmias (irregular heartbeats). These often go away on their own, but may need treatment if they persist.
- Damage to the kidneys caused by the dye used.
- Blood clots that can trigger stroke, heart attack, or other serious problems.
- Low blood pressure.
- A build-up of blood or fluid in the sac that surrounds the heart. This fluid can prevent the heart from beating properly.

Subjects will receive ten infusions of CER-001 (3mg/kg) or placebo during the study. CER-001 has been well tolerated in the five clinical studies conducted to date. In the only double-blind trial, there were more SAEs and AEs leading to discontinuation in the active treatment groups, mainly due to the occurrence of infusion reactions. Treatment-related infusion reactions, either local injection site reactions or other more generalized reactions, have occurred in 16 subjects during Phase II studies. These reactions were reversible in all cases and either resolved spontaneously or after management with antihistamines, steroids and/or IV fluids. 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. Clinical study sites should be aware of the possibility of infrequent infusion reactions and be prepared to provide supportive care if necessary.

The encouraging efficacy results seen to date in the CHI SQUARE, MODE and SAMBA studies indicate a potential important benefit for subjects (regression of atherosclerotic disease) and warrant further clinical studies.

3.7 Dose Selection

Results from the CHI SQUARE study indicate that 3 mg/kg is the optimal dose of CER-001 for the treatment of ACS (see Section 3.4 Clinical Findings for CER-001). Efficacy was not enhanced by increasing individual doses to 6 or 12 mg/kg, in fact there was an inverse dose-response. This phenomenon has also been seen preclinically for CER-001, both in an in vitro cholesterol efflux model and in an in vivo carotid “flow-cessation” study using the apoE -/- (“knockout”) mice. In the cholesterol efflux model, ABCA1 expression was down-regulated with increasing CER-001 dose and a consequent reduction in ABCA1-medicated cholesterol efflux from J774 macrophages was observed. In the mouse model, the carotid cholesterol content exhibited a U-shaped dose-response curve, with a maximum effect seen 5 mg/kg dose.

The CHI SQUARE study used a series of 6 dose administrations spaced one week apart. The SAMBA study had an intensive “induction” period of dosing every 3 days for a month, followed by a maintenance phase with biweekly dosing for an additional five months. There was some evidence of accumulation of apoA-I with q 3 day dosing, however significant reduction in carotid and aortic plaque, measured by mean vessel wall area, was observed at the end of the induction period. Subsequent bi-weekly dosing maintained the effect but did not result in significant further reduction. The present study will combine the learnings from CHI SQUARE and SAMBA and evaluate a
regimen of 3 mg/kg per dose with a series of ten doses given once weekly over a nine-week period.

3.8 GCP Statement

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki (See Appendix B) and in compliance with current Good Clinical Practices (cGCPs; ICH E6), local regulatory requirements, and the requirements of the US Food and Drug Administration (21 CFR 312).

3.9 Population to be studied

Subjects undergoing clinically indicated coronary angiography, who either present within 7 days of acute chest pain or other angina equivalent symptoms indicative of a diagnosis of ST segment elevation myocardial infarction, non-ST elevation myocardial infarction or unstable angina. The unstable angina cohort will be capped at approximately 25% of randomized subjects. Subjects must be able to be randomized into the study within 14 days of presentation with ACS.

3.10 Literature Review

Cardiovascular disease remains the most pressing healthcare issue for developed countries and is becoming so for developing countries. There are a number of chronic therapies available for long-term management of risk. Short-term therapies for subjects with an acute event, such as an episode of ACS or myocardial infarction (MI) are focused on reperfusion and removing thrombus but most subsequent events are caused by plaque rupture at a different site. There are no approved therapies that can rapidly reduce the burden of unstable, inflamed plaque in the overall coronary vascular bed. HDL has multiple actions that could lead to plaque stabilization, such as rapid removal of large quantities of cholesterol from the vasculature, improvement in endothelial function, protection against oxidative damage and reduction in inflammation.

CER-001 is an HDL-like discoidal particle based on a combination of a recombinant full length apoA-I and a proprietary lipid composition that should mimic most, if not all, of the effects of native HDL particles, most importantly rapid mobilization and elimination of cholesterol from the vessel wall following intravenous infusion. Cerenis intends to develop CER-001 for the acute management of subjects presenting with the sequelae of unstable coronary plaque. It is not anticipated that the short-term use of CER-001 complexes will lead to a long- or even medium-term increase in HDL levels. Rather, it is
expected that there will be an acute mobilization of cholesterol from the vascular bed, which will lead to plaque reduction and stabilization.

Three clinical studies, two with different forms of synthetic HDL [ETC-216, recombinant apoA-I Milano/palmitoyl-oleoyl-phosphatidyl-choline (POPC) complexes and CSL-111, reconstituted purified human apoA-I from outdated plasma complexed with soy bean phosphatidyl-choline (SBPC)] and one with autologous delipidated HDL, have validated the concept that short-term use (4 to 7 infusions) of synthetic HDL particles can lead to rapid plaque regression as determined by IVUS evaluation. In addition to the three IVUS studies, six other clinical studies have been conducted with infused synthetic HDL evaluating acute effects on plasma lipids, fecal sterol excretion, endothelial function, glucose levels in diabetics, and changes in excised femoral artery plaque. The published results from these nine studies are reviewed in the following sections.

3.10.1 Acute Effects of Synthetic HDL on Plasma Lipoproteins

To investigate the metabolism of nascent HDL, purified human apoA-I/SBPC discs were infused IV over 4 hours into 7 healthy male subject⁶. Three subjects received the low dose (25 mg/kg) and four subjects received high dose (40 mg/kg) therapy. Plasma total apoA-I and phospholipid (PL) concentrations increased during the infusions. The rise in plasma apoA-I was greatest in small pre-β migrating particles not present in the infusate. Total HDL unesterified cholesterol (UC) also increased during the infusion. After the end of the infusion, the concentrations of apoA-I, PL, HDL UC, and small pre-β HDLs decreased, whereas those of HDL cholesterol ester (CE) and large α migrating apoA-I containing HDL increased. ApoB containing lipoproteins became enriched in CE (Figure 1). Infusion of discs also reduced the plasma apoB and apoA-II concentrations, and increased plasma triglycerides and apoC-III.

Several in vitro experiments were conducted to clarify the mechanisms of the changes observed in vivo. Addition of purified human apoA-I/SBPC discs to whole blood at 37°C in vitro also generated small pre-β HDL, but did not augment the transfer of UC from erythrocytes to plasma.

The authors thereby concluded that the disc infusions increased the intravascular production of small pre-β HDL in vivo, and that this was associated with an increase in the efflux and subsequent esterification of UC derived from tissue.
Figure 3. Changes in the concentrations of total cholesterol, UC, CE, TG, and PL in whole plasma, HDLs and non-HDL lipoproteins in the 4 subjects given the high-dose infusion. Results (means ± SEM) are the differences between the concentration at each time point and the baseline concentration; *p<0.05. HDLs and non-HDL lipoproteins were separated by PEG.

3.10.2 Effect of Synthetic HDL on Fecal Sterol Excretion

The effect of an intravenous infusion of 4g of recombinant human pro apoA-I complexed with SBPC, infused over 20 minutes, was studied in four subjects with phenotypical heterozygous familial hypercholesterolemia under standardized conditions. The fecal excretion of bile acids and neutral sterols was determined for 9 days before and 9 to 12 days after the infusion. Plasma apoA-I and HDL cholesterol levels increased transiently (mean peak concentrations were 64% and 35% above baseline, respectively) during the first 24 hours.
Fecal sterol excretion (FSE; neutral sterols and bile acids) increased in all subjects (mean increase, 39% and 30%, respectively), corresponding to the removal of ~500 mg/d excess cholesterol after infusion. Control infusions with liposomes only in 2 of the subjects did not influence lipoprotein pattern or cholesterol excretion. The authors concluded that infusion of pro apoA-I/SBPC complexes in humans promotes net cholesterol excretion from the body, implying a stimulation of reverse cholesterol transport.

The effect of CER-001, 8 mg/kg infused over 60 minutes, on FSE was studied in 4 subjects with genetically-confirmed FPHA who participated in the SAMBA study (Kootte et al. 2015, op cit). Before and after CER-001 infusion, FSE was determined for a total of eight days. Subjects were maintained on a cholesterol-restricted diet, ingested 3mg D4-sitostanol TID and stool was collected daily. Sitostanol was used to correct for variations in fecal flow, as it is not absorbed by the intestines. The daily FSE was calculated as relative amounts compared to the daily excretion of D4-sitostanol. Daily sterol excretion was added together to determine total sterol excretion during the experiment.

After CER-001 treatment there was a trend towards increased FSE (from 8.94 [6.43 – 11.76] to 10.11 [6.81 – 12.91] g; p=0.068), corresponding to an extra 0.68 [0.38 – 1.65] g of sterols being excreted during 8 days after treatment. This trend was caused by enhanced neutral sterol excretion (p=0.068), whereas bile acid excretion was unaffected (p=0.715). FSE increased in all four subjects studied following CER-001 infusions.

4 TRIAL OBJECTIVES

To assess the impact of ten intravenous infusions of 3 mg/kg CER-001 vs. placebo, given at weekly intervals, on atherosclerotic plaque volume, as measured by coronary IVUS, when administered to subjects presenting with an Acute Coronary Syndrome (ACS) event.
5 TRIAL DESIGN

5.1 Primary Efficacy Parameters

The primary efficacy parameter for this study is the nominal change from baseline to follow-up in the percent atheroma volume (PAV) in the target coronary artery assessed by 3-dimensional (3D) IVUS. The primary endpoint will be a comparison of the primary efficacy parameter between randomized treatment groups (Placebo vs. CER-001 3mg/kg) using an analysis of covariance (ANCOVA) with adjustment for baseline PAV. The adjusted mean endpoint in each treatment group and the difference in means (95% confidence interval) will be presented. Statistical significance will be assessed at the alpha=0.05 level. For further statistical information see Section 11.

5.2 Secondary Efficacy Parameters

Secondary atherosclerosis efficacy parameters will include the (i) nominal change from baseline to follow-up in normalized total atheroma volume (TAV) and (ii) nominal change in TAV in the 10-mm sub segment of the coronary artery with the largest plaque volume at baseline (the most diseased segment).

5.3 Exploratory Efficacy Parameters

- Pre- to post-dose changes in lipoprotein profiles by HPLC at the first and last doses.
- Pre- to post-dose changes in apoA-I levels at the first and last doses.
- Pre- to post-dose changes in cellular cholesterol efflux capacity at the first and last doses.
- Pre-dose lipid profiles, including low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol (TC), free cholesterol (FC), triglycerides (TG), phospholipids (PL), apolipoproteinA-I (apoA-I) and apolipoprotein B (apoB), will be determined periodically throughout the study (see Appendix A).
- Baseline to follow up changes in any plaque characteristic measurements taken during the IVUS procedure

Episodes of all death (to determine whether cardiovascular death occurred), non-fatal myocardial infarction, resuscitated cardiac arrest, non-fatal stroke, fatal stroke, coronary revascularization procedures [percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)], hospitalization for unstable angina, hospitalization for congestive heart failure (CHF), any admission for a procedure for the treatment of PVD (including cerebrovascular procedures) and urgent readmission with chest pain (to
determine whether a diagnosis of MI or unstable angina should be made) will be recorded by the Investigator using electronic Case Report Forms (eCRFs). The events will be reviewed and adjudicated by the Clinical Endpoint Committee (CEC) according to established definitions. This study is not powered for MACE endpoints.

5.4 Summary of Trial Design

It will involve approximately 40 study sites in Australia, the United States, Netherlands and Hungary. It is expected that approximately 600 subjects will be screened and will have a baseline IVUS assessment in order to randomize approximately 292 subjects (146 in each treatment arm of the study).

Subjects will be required to have at least one epicardial coronary artery suitable for IVUS imaging. A suitable target artery for IVUS imaging will be determined at baseline as having stenosis of up to 50% and meeting all angiographic inclusion criteria. Subjects having met all eligibility criteria including acceptance of the baseline IVUS by the IVUS Core Laboratory for overall quality and >30% PAV in the most proximal 10 millimeters, will be randomized to receive an intravenous infusion, given over 30 minutes, of placebo or CER-001 (3 mg/kg).

Randomization must occur within 14 days of the ACS event. Randomized subjects will return at 7-day intervals (i.e., window of +/- 2 days) for nine additional infusions. End-of-treatment labs will be drawn 7 days (window of +/- 2 days) after the last infusion. A follow-up IVUS will be conducted at 14 days (i.e., window of +/- 7 days) after the last infusion. The anticipated length of study for an individual subject is planned to be 84 days, but may range from 53 to 103 days depending on actual visit dates.
Figure 4. Schematic study design.

![Schematic Study Design]

Figure 5. Schematic of subject’s participation in the study.

![Schematic Subject Participation]

An overview of the study procedures performed at each study visit is presented in Appendix A.
5.5 Minimizing Bias

5.5.1 Randomization

After obtaining written informed consent, completing screening procedures, and ensuring the subject meets all of the inclusion criteria and none of the exclusion criteria, the study site must await notification that the screening IVUS is approved by the Core Laboratory. Once this is received via the EDC system, the subject will then be randomized. The subject will be randomised to receive ten infusions of either active drug or placebo.

5.5.2 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 subject 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.

5.6 Treatment Summary

5.6.1 Pharmaceutical Properties and Formulation

The study drug, CER-001 Sterile Solution for Infusion, is a solution of the apoA-I/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

<table>
<thead>
<tr>
<th>International Non-Proprietary Name (INN)</th>
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<td>United States Adopted Name (USAN)</td>
<td>To be determined</td>
</tr>
<tr>
<td>CAS Number</td>
<td>1383435-67-3</td>
</tr>
<tr>
<td>Laboratory Code</td>
<td>CER-001</td>
</tr>
<tr>
<td>Description (Drug Substance)</td>
<td>Protein/phospholipid complex containing a1:2.7 weight to weight ratio of recombinant human apoA-I to phospholipids (97% Sph, 3% DPPG)</td>
</tr>
<tr>
<td>Physical Form (Drug Product)</td>
<td>Solution of the apoA-I/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.</td>
</tr>
<tr>
<td>External Appearance</td>
<td>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</td>
</tr>
<tr>
<td>Storage Conditions</td>
<td>Store frozen at -15C to -25C; thaw before administration. A matching placebo of normal saline will also be supplied.</td>
</tr>
</tbody>
</table>

5.6.2 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.

5.6.3 Medication Dispensing and Administration

The Investigator will administer the study medication only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given
only the study medication assigned by the randomization system. All dispensing will be documented in the Case Report Form (CRF) and other study drug records.

5.6.4 Method of Administration

CER-001 will be supplied as a frozen sterile solution in 20 ml glass vials. CER-001 will be constituted into an IV dosing solution by the Study Pharmacist or designee by diluting with normal saline. Normal saline alone will be used as the placebo. The Study Pharmacist or designee will dispense the appropriate concentration and volume of solution (active drug or placebo) for each subject, based on his/her weight at Screening. The pharmacist will add the required amount of CER-001 for each subject to an empty 250 mL infusion bag and then make up the total volume to 125 mL using normal saline. The infusion bag and drip set will be sent from the pharmacy with the infusion bag shrouded with a bag to maintain the blind. The rate of infusion will be the same for all subjects, 250 mL/hr. Study drug will be infused over a 30 minute period. Study drug administration may be extended up to a period of 120 minutes if deemed medically necessary for the subject by the Investigator (e.g. concern for fluid overload). Reasons for administration periods greater than 30 minutes must be properly documented. A normal saline administration set will be used to maintain venous access for 30 minutes after the infusion is complete.

5.6.5 Additional Supplies Provided by Sponsor

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

5.6.6 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 unobiterated. The “Clinical Returns Authorization Form” contains a specific return shipping address and instructions.
5.7 Trial Duration

This will be a phase II, multicenter, double blind, placebo-controlled trial. As outlined in Appendix A, the study consists of:

1. Screening Period  1 to 14 days prior to dosing (SCR and BLIVUS visits)

2. Treatment Period  Up to 90 days (10 infusion visits separated by 7 days (with window of +/- 2 days); RINF1, INF2, INF3, INF4, INF5, INF6, INF7, INF8, INF9, INF10 visits)

3. Follow-up Period  Up to 21 days (EOTP and FIVUS visits)

4. Safety Follow-Up  30 days (window of +/- 5 days) post-INF10 via telephone call

The minimum duration from randomization to study end will be approximately 53 days for an enrolled subject who completes the trial as designed.

5.8 Stopping Rules

Since this study is based on the surrogate measure of coronary plaque volume and the relationship between changes in plaque volume and mortality has not been established, there will be no stopping rules for efficacy. The Investigator (or designee) will review all safety data for each subject enrolled at his site after each infusion.

The Data Safety Monitoring Board (DSMB) will formally review study safety data to ensure there is no avoidable increased risk for harm to subjects. 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 a group which is external to Cerenis. In addition, Cerenis performs continuous monitoring of SAEs in a blinded manner.

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 an adverse event of special interest (allergic/infusion reaction or LFT 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.

Subjects should have dosing withheld if the most recently obtained serum ALT exceeds five times the upper limit of normal. If the most recently obtained serum ALT elevation is greater than the upper limit of normal but less than five times the upper limit of normal, the subject may receive their next dose, which may be reduced in consultation with the CARAT medical monitor (see Section 10).

Subjects are to be permanently discontinued from the study drug if:

1. They experience a simultaneous elevation in serum ALT greater than three times the upper limit of normal and serum total bilirubin greater than two times the upper limit of normal without an obvious cause (e.g. passing a gall stone, acute viral hepatitis). These results should be confirmed by repeat testing.
2. They experience two consecutive elevations in serum ALT exceeding five times the upper limit of normal without an obvious cause.
3. If they experience an elevation in serum ALT exceeding three times the upper limit of normal for more than three weeks with no obvious cause.

In the case of any of these abnormalities, subjects should be retested at the earliest possible time point to confirm the liver enzyme abnormalities. If the repeat results no longer meet the above criteria, individual subject continuation will be reviewed and discussed with the study Medical Monitor and Investigator. In cases where an explanation other than study drug is determined to account for hepatic abnormalities, the cause should be thoroughly documented in the subject record.

In order to assist in the evaluation of liver enzyme abnormalities, the Investigator, Medical Monitor and a Cerenis representative must be notified by the testing laboratory via phone, email or fax within 24 hours if ALT or AST results are greater than 3 times the upper limit of normal and/or if total bilirubin is greater than two times the upper limit of normal.

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
   c. Creatinine Clearance ≤ 30mL/min.

Creatinine clearance will be measured from serum creatinine based on the Cockcroft-Gault formula:
CrCl = \( \left[ \frac{140 - \text{age (years)}}{72 \times \text{serum creatinine (mg/dL)}} \right] \times \text{weight (kg)} \times 0.85 \text{ for female subjects} \)

The Investigator, Medical Monitor and a Cerenis representative will be notified by the testing laboratory via phone, email or fax if serum creatinine is greater than 1.5 times the upper limit of normal. In the case of any of these abnormalities, subjects should be retested at the earliest possible time point.

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 subject record.

**5.9 Maintaining Study Blind**

Study drug will be dispensed by the Study Pharmacist or designee who will be unblinded as described in Section 5.6.3 Medication Dispensing and Administration. The study subjects, Investigator and study site personnel, site monitors and Medical Monitor will remain blinded to the treatment. A representative from the Sponsor will be unblinded to study 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 to the extent possible and all blind breaks will be documented.

The double-blind code may be broken only in the case of a major medical emergency when the information is necessary for proper subject management and permission given by the authorized Project Medical Officer. If a blind is broken, the date, time, and a detailed reason must be documented. The database will be cleaned and locked after the final data is entered, and the data will be unblinded and analyzed for all primary and secondary efficacy and safety parameters.

**6 SELECTION AND WITHDRAWAL OF STUDY SUBJECT**

**6.1 Inclusion Criteria**

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

1. Subjects must provide informed consent, as approved by the IRB/EC prior to performance of any screening procedures
2. Male or female at least 18 years of age
3. Subject of non child-bearing potential,
   a) Greater than 12 months since last menstrual period; and/or surgically sterilized and agree to use barrier method of birth control for the entire study; and/or
   b) On hormonal therapy (including implants, injections, combined oral contraceptives and IUDs) and agree to use a barrier method of birth control for the entire study: and/or
   c) Agree to use a double barrier method of birth control defined as condom in combination with diaphragm, contraceptive sponge, spermicidal foam or cervical cap.

4. Subjects who undergo coronary angiography within 7 days of presentation with ACS:

   **ACS Criteria Myocardial Infarction**
   a) Cardiac biomarkers (troponin I or T, CKMB mass, or CK-MB activity) with at least one determination > 99th percentile or above the local laboratory upper reference limit
   AND one of the following:
   b) Chest pain or ischemic symptoms at rest >10 minutes within prior 24 hours
   c) New ECG changes of acute ischemia (LBBB, ST elevations, or ST depressions)
   d) New pathologic Q-waves or R/S >1 in V1- V2
   e) Regional myocardial scar or ischemia by nuclear, magnetic resonance, echocardiographic, or angiographic imaging

   **OR Biomarker-Negative ACS (Unstable Angina)**
   a) No elevation of cardiac biomarkers
   b) Chest pain or ischemic symptoms at rest >10 minutes
   c) Prompting Hospitalization or chest pain observation unit within 24 hours of symptoms
   AND one of the following:
   d) New or worsening ECG changes (transient ST elevation, ST depression, or T inversion)
   e) Definite myocardial ischemia on nuclear or echocardiographic imaging
   f) Angiographic stenosis >70% or thrombus in epicardial coronary artery or bypass graft and/or performance of PCI

5. Baseline Coronary angiogram must meet all the following criteria for IVUS interrogation of Target Artery;
**Target Artery:**
- a) Must be accessible to the IVUS catheter
- b) Must have a stenotic area of ≤50% in lumen diameter by angiographic visual estimation within the length of the native coronary artery for imaging by IVUS
- c) The target artery may not be a bypass graft
- d) The target artery may not be the culprit vessel for a previous MI

**Target Artery May Have:**
- a) A lesion up to 60% stenosis, distal to the target segment, provided that this area is not anticipated to be a target for PCI or CABG during the course of the study
- b) A single branch of the target artery may have a narrowing ≤70% by visual estimation, provided that the branch is not a target for PCI or CABG during the course of the study

6. Subject is able to be randomized within 14 days of ACS event presentation
7. Baseline IVUS interrogation determined to be of acceptable quality with PAV ≥ 30% in the proximal 10mm at review by the Imaging Core Lab
8. Subject must be willing to participate in the study and comply with all protocol requirements, including willingness to:
   - a) Return to the clinic weekly for a total of ten IV infusions of study drug
   - b) Return to the clinic for follow up visits
   - c) Return to the clinic at the end of the study for follow up IVUS procedure

### 6.2 Exclusion Criteria

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

1. Baseline IVUS not completed due to non-qualifying coronary angiogram as demonstrated by:
   - a) Greater than 50% reduction in lumen of the left main coronary artery by visual estimation
   - b) Extensive coronary artery disease with no target vessel for IVUS interrogation
   - c) Angiographically normal coronary arteries
2. Baseline IVUS interrogation determined to be unacceptable by the Imaging Core Lab
3. Subjects with uncontrolled diabetes defined as HbA1c > 10% at Screening
4. Subjects with triglycerides >500 mg/dL at Screening
5. Subjects with coronary artery bypass graft (CABG) surgery in previous 6 weeks or in whom CABG is planned
6. Myocardial infarction in the target coronary artery for IVUS between the initial IVUS examination and randomization
7. Subjects who have symptomatic congestive heart failure (CHF) (New York Heart Association [NYHA] Class III or IV) at baseline
8. Subjects with a known ejection fraction <35% (investigations to document EF not required)
9. Subjects with clinically significant valvular heart disease likely to require surgical repair or replacement during the treatment period of the study
10. Subject is hemodynamically or clinically unstable in the opinion of the Investigator.
11. Subject has uncontrolled hypertension (e.g., sitting systolic BP > 180 mm Hg on antihypertensive therapy) at time of randomization
12. Subject has known major hematologic, hepatic (liver enzymes greater than twice the upper limits of normal for the performing laboratory), metabolic, gastrointestinal or endocrine dysfunction in the judgment of the Investigator
13. Subject has known renal dysfunction CrCl ≤ 30mL/min
14. Any clinically significant medical condition or presence of any laboratory abnormality performed prior to randomization that is considered by the investigator to be clinically important and could interfere with the conduct of the study
15. Subject is likely to be unreliable as a study participant based on the Investigator's (or designee’s) knowledge of the subject (e.g., alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis)
16. Subject has participated in any investigational drug or interventional device study within 30 days prior to randomization, or expects to participate in any other investigational drug or interventional device study during his/her planned participation in this study
17. Subject has previously participated in this study or another study involving CER-001.

6.3 SUBJECT RESTRICTIONS DURING THE STUDY

There are no subject restrictions other than those outlined in the Inclusion/Exclusion criteria above.

6.4 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 subject non-compliance
- Subject’s request, for tolerability reasons
- Subject’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.

Subjects should continue to be followed as though they had completed the treatment phase. Subjects who prematurely (i.e., prior to completion of the tenth infusion) discontinue study medication are to be followed for the remainder of their follow-up period and should undergo all subsequent visit evaluations, including the follow-up IVUS evaluation whenever possible.

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

A discontinuation occurs when an enrolled subject 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 (Section 9.1). A discontinuation must be reported immediately to the Sponsor (or designated representative) if it is due to a serious adverse event (see Section 10.6).

If a subject discontinues treatment, the end of study evaluations (FIVUS Visit procedures), including safety assessments, required by the protocol should be performed as per the study schedule. The Investigator will record the reason for study drug discontinuation, provide or arrange for appropriate follow up for such subjects, and document the course of the subject’s condition during the appropriate follow up period on the follow up contact Case Report Form (CRF).

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

7 TREATMENT OF SUBJECTS

7.1 Investigational Product

Dosing will occur at the Randomization and First Infusion Visit (RINF1) and at weekly Infusion visits, every 7 days, (INF2, INF3, INF4, INF5, INF6, INF7, INF8, INF9, and INF10) for a total of ten doses. At each of these visits, subject will be given a single IV infusion of either placebo
or CER-001 (3mg/kg) over a 30 minute period. Dosing procedures are specified in Section 5.6.4 (Method of Administration).

7.2 Interruption or Discontinuation of Study Medication

Subjects 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 subject’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 subject 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.

7.3 Dose Adjustments in 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 (RINF1 Visit). 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 125 mL of study drug solution to be administered over 30 minutes. Complete instructions for preparation of reduced doses will be contained in the Pharmacy Manual.

The investigator may increase the subject 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 subject receive a dose greater than the prescribed dose.

7.4 Concomitant Treatments

Any medication the subject takes, other than study drugs specified by the protocol, is considered a concomitant medication. All concomitant medications must be recorded in the CRF.
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 subject health are permitted during the study. Details of their use must be recorded on the concomitant medication page of the CRF.

7.7 Plasma Lipid Control

In the absence of a clinical reason to the contrary, it is recommended that subjects’ lipid levels be maintained in accordance with the appropriate local national guidelines for control of cholesterol lowering therapy in subjects with known coronary artery disease, consistency in the subjects' current treatment is recommended over the course of the study.

7.8 Monitoring of Subject Compliance

All study therapy will be administered under direct observation.

8 ASSESSMENT OF EFFICACY

8.1 Efficacy Parameters

Efficacy parameters will include IVUS evaluations of coronary plaque burden, lipid profiles, as well as several exploratory biomarkers for efficacy.

8.2 Methods and Timing for Assessing Efficacy Parameters

8.2.1 IVUS Evaluations

The detailed procedure for collection of coronary IVUS data will be outlined in the IVUS Imaging Manual. The baseline IVUS can be performed at any time during the screening period, prior to study randomization. Subjects will be required to have at least one epicardial coronary artery suitable for IVUS imaging. A suitable target artery for IVUS imaging will be determined at baseline as having stenosis up to 50% and meeting all angiographic inclusion criteria. The baseline IVUS will need to be accepted by the IVUS Core Laboratory for overall quality, the presence of a suitable target vessel and the absence of technical factors which can preclude accurate reading of the IVUS images. The IVUS Core Lab will determine if a PAV of ≥30% in the most proximal 10 millimeters is evident to meet the inclusion criteria for randomization.
Once this baseline IVUS has been approved by the Core Laboratory, the subject may be randomized.
A follow up IVUS will be conducted at 14 days (with a window of +/- 7 days) after the final infusion.

8.2.2 Lipid Profiles

Fasting samples for the following lipid profile tests will be obtained at SCR (Triglyceride only), RINF1 and INF10 (pre and post infusion), INF2, INF3, INF4, INF5, INF6, INF7, INF8, INF9, EOTP, FIVUS and SMFU visits:
Total Cholesterol
Unesterified Cholesterol
LDL Cholesterol (RINF1 Pre-dose, FIVUS and SMFU)
HDL Cholesterol (RINF1 Pre-dose, FIVUS and SMFU)
Triglycerides
Phospholipids
apolipoprotein A-i
apolipoprotein B

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.

9 ASSESSMENT OF SAFETY

9.1 Safety Parameters

All subjects who receive study medication and have a subsequent safety evaluation will be included in the safety analyses.

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. AEs of special interest will include infusion/allergic reactions and liver enzyme elevations. Case summaries will be provided for these cases, as well as AEs leading to withdrawal, serious AEs and any events not considered AEs because they are determined to be MACE.

Adverse events will also be tabulated by study treatment. Summary tables will give the number and proportion of subjects 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 SCR and at the FIVUS visits. Shift tables of these values will be provided to summarize the change between SCR and the FIVUS visit for each treatment group. Safety parameters include physical examinations, vital signs, electrocardiograms, clinical laboratory tests, as well as routine monitoring for adverse events (see Section 10). All clinical laboratory will be performed by central laboratories.

9.2 Methods and Timing for Assessing Safety Parameters

9.2.1 Physical Exam

The Investigator or qualified designee will perform a complete physical examination at the SCR and FIVUS visits. Height and weight will be collected at the SCR 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 SCR visit will be noted and if adverse and clinically significant, in the judgment of the Investigator, will be reported on the adverse event form.

9.2.2 Vital Signs

Temperature and respiratory rate (RR) should be measured at the SCR visit. Temperature should be recorded in degrees centigrade. 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 subject’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 SCR visit, randomization, pre-infusion and post-infusion (after the post-infusion observation period prior to the subject leaving the clinic) at visits RINF1, INF2, INF3, INF4, INF5, INF6, INF7, INF8, INF9, INF10 and FIVUS visit. BP and HR measurements should be determined after the subject has been seated for at least 5 minutes. At the SCR 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 subject has a SBP reading of >180mmHg at time of randomization the Investigator, in consultation with the subject may measure again if able to randomize within the allowed window.

**9.2.3 Electrocardiograms**

Protocol-specified ECGs will be acquired. 12 lead ECGs will be performed using equipment on site at RINF1 (pre-infusion and at the end of infusion) and FIVUS visits. The Investigator will perform standard interpretations of all tracings with results documented in the appropriate source documents and CRFs. The ECG report will be de identified and uploaded into the eCRF for delivery to the database.

It is the responsibility of the Investigator to obtain additional ECGs required for the clinical management of the subject. 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 and submitted to the C5 safety desk as part of the documentation package for clinical endpoint adjudication if requested.

**9.2.4 Clinical Laboratory Tests**

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. SAHMRI will perform exploratory lipid and inflammatory markers of atherosclerosis taken at randomization and final IVUS visit. Results from this analysis will be documented and maintained, but may not be reported as part of this study. There is no genetic/genomic testing. Specific information regarding the number and type of blood collection tubes will be provided in the Lab Manual.

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. A serum pregnancy test will be done at SCR and FIVUS on pre and perimenopausal females (less than 12 months since last menstrual period). 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
Aspartate Aminotransferase (AST/SGOT)
Alanine Aminotransferase (ALT/SGPT)
Alkaline Phosphatase
Total Protein
Albumin
Globulin
Lactate Dehydrogenase (LDH)
Creatine Kinase (CK)
Sodium
Potassium
Chloride
Carbon dioxide
Uric Acid
Calcium
Phosphorous
C - reactive protein
Hemoglobin A1c (HbA1c)

HEMATOLOGY

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

URINALYSIS

Microalbuminuria
Specific Gravity
pH
Glucose
Total Protein
Blood
Ketones
Total Bilirubin
WBC
RBC
Hyaline Casts
Granular Casts
WBC Casts
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 as follows:

1. Test result is confirmed upon repeat (unscheduled) testing, and
2. Test result is associated with accompanying symptoms, and/or
3. Test result requires additional diagnostic testing or medical/surgical intervention, and/or
4. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
5. Test result leads to any of the outcomes included in the definition of a serious adverse event, and/or
6. Test result is considered to be an adverse event by the Investigator for other reasons (which should be documented)

Repeating an abnormal test, in the absence of any of the criteria listed above, does not meet the criteria for reporting as an adverse event.

9.2.5 Immunogenicity Testing

Specimens will be collected for anti-apoA-I antibody testing at the BLIVUS, INF4, INF10 and FIVUS visits. If subjects have a positive result at the FIVUS they must return monthly for testing until the antibodies return to baseline. The Anti-apoA1 antibody testing will be performed by the central laboratory. 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-apoA1 antibody testing will be analyzed for neutralizing antibody activity.

10 ADVERSE EVENT REPORTING

All observed or volunteered adverse events occurring at any time following consent and screening, regardless of treatment group or suspected causal relationship to study drug, will be recorded on the adverse event page(s) of the CRF.

10.1 Definition

An adverse event (AE) can be any unfavorable and unintended sign including an abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the study drug. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbation’s of pre-existing illnesses should be recorded. 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 subject 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.

For all adverse events, the Investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the Medical Monitor (see Section 10.6). For all adverse events, sufficient information should be obtained by the Investigator to determine the causality of the adverse event (e.g., study drug or other illness). The Investigator is required to assess causality and indicate that assessment on the CRF. Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator and the Medical Monitor. Satisfactory resolution may also include referral to the subject’s PMD for follow-up.

10.2 Severity Rating

Assess the severity of an AE 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

10.3 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 subject 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).

10.4 Expected Side Effects

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

Side effects 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 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.

10.5 Reporting
Record all clinical events, including either observed or volunteered problems, complaints, or symptoms on the AE page(s) of the CRF. The need to capture this information is not dependent upon whether the clinical event is associated with the use of the study drug. Also, record adverse clinical events resulting from concurrent illnesses or reactions to concurrent medications. In order to avoid vague, ambiguous, or colloquial expressions, record the AE in standard medical terminology rather than the subject’s own words. Evaluate each adverse clinical event for duration, severity, association with the study drug or other cause, and seriousness (see Section 10.6). Record start and stop dates, relationship to study drug, medical management, and outcome of the AE on the AE CRF(s). Follow AEs that are believed to be at least possibly related to study drug until satisfactory resolution.

10.6 Serious Adverse Events

10.6.1 Definition
A serious adverse event is any adverse drug experience occurring at any dose that:
1. Results in death;
2. Is life threatening;
3. Results in subject’s hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability/incapacity; or
5. Results in congenital anomaly/birth defect

Events that are identified as major adverse cardiovascular events (MACE) listed as exploratory endpoints will NOT be reported as SAEs unless it is determined by the CEC that the event does not meet the pre-defined criteria for an endpoint of MACE according to established definitions. MACE events adjudicated by the CEC as non endpoints will be evaluated for seriousness according to the definition above and will be reported according to the requirements and timeframe described below.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse drug experiences when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 subject hospitalization, or the development of drug dependency or drug abuse. Regardless of the above criteria, any additional adverse experiences which the Sponsor, ARO, or an Investigator considers serious should be immediately reported to the C5 safety desk and will be included in the serious adverse events database for CER-001.

A life-threatening adverse event is any adverse drug experience that places the subject 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 subjects, 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”, but is not an adverse experience 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., subject 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).

However, if a hospitalization for an unknown event occurs, it should be considered as a serious adverse event.

Inpatient admission does not include the following:
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
9. Custodial care facilities
10. Clinical research/Phase I units
Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the Investigator or treating physician. For protocol-specified hospitalizations in clinical trials, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical adverse event (e.g., not associated with the development of a new adverse event or worsening of a pre-existing condition) may meet criteria for “seriousness”, but is not an adverse experience and thus is not subject to immediate reporting.

Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Disability is a substantial disruption of a person’s ability to conduct normal life functions.

Any serious adverse event or death must be reported immediately, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the Investigator at any time following randomization through the last follow-up visit required by the protocol or thirty (30) days after the last administration of study drug, whichever comes later. Any serious adverse event occurring at any other time after completion of the study must be promptly reported if a causal relationship to study drug is suspected.

A medical hotline will be available 24 hrs a day, 7 days a week for the duration of the study. The hotline physician will remain blinded and is able to liaise with Cerenis in the case unblinding may be necessary.

For all serious adverse events, the Investigator is obligated to pursue and provide information as requested by the Sponsor or Medical Monitor in addition to that on the CRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, including concomitant medications and illnesses, must be provided. The Investigator's assessment of causality must also be provided. If causality is unknown, it should be attributed to study drug. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Medical Monitor. The Investigator should ensure that all serious adverse events are reported to the IRB/IEC and Sponsor and information reported immediately by telephone or other means and information entered in the CRF are accurate and consistent.

10.6.2 Reporting

Report any SAE, occurring in a subject receiving study drug or within 30 days of the last dose of study drug, to the Central Safety laboratory, C5, **within 24 hours even if the SAE does not appear to be drug-related**. Report the information via the eCRF or by telephone **and** either by sending a faxed copy or e-mailing a PDF copy of the Sponsor’s Serious Adverse Event Form plus other supporting information as necessary.
Report all additional follow-up evaluations. Send such data to C5 within 10 working days. Follow all SAEs until the Investigator/Medical Monitor/Sponsor agree the event is satisfactorily resolved. The Medical Monitor and/or Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the ICH Guidelines. The Medical Monitor and/or Sponsor will also notify all other Investigators participating in studies of CER-001 as required by regulations. The Investigator is responsible for notifying his/her IRB/IEC directly.

**10.7 MAJOR ADVERSE CARDIOVASCULAR EVENTS**

Suspected major adverse cardiovascular events (MACE) will be collected by the Investigator and adjudicated by the CEC to the following conditions:
1. Cardiovascular death
2. Non-fatal myocardial infarction
3. Resuscitated cardiac arrest
4. Coronary revascularization procedures (PCI, CABG)
5. Hospitalization for unstable angina
6. CHF event (urgent visit and hospitalization)
7. Fatal and non-fatal strokes
8. Any admission for a procedure for the treatment of PVD (including cerebrovascular procedures)

**10.8 Pregnancy**

Notify the Medical Monitor if a subject becomes pregnant. Pregnancy itself is not an AE; however pregnancies must always be followed until completion or until pregnancy termination (i.e. induced abortion) and the Medical Monitor must be notified of the outcome. The Investigator will be provided with a Pregnancy Report Form. This form must be completed and returned to the Medical Monitor. 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 reporting SAEs. Record any complications during pregnancy as AEs and/or SAEs.

**10.9 Follow-up of Subjects after Adverse Events**

When a serious or at least possibly related AE persists at the end of the study, the Investigator will ensure a follow-up of the subject until the Investigator and Sponsor agree the event is satisfactorily resolved. Satisfactory resolution may include referral to the subject’s usual care provider.
11 STATISTICS

11.1 Statistical Methods

Data will be analyzed by The South Australian Health and Medical Research Institute (SAHMRI). All cases will be checked for consistency and completeness by the Data Management Department of SAHMRI. All statistical tests will be assessed at $\alpha=0.05$ level of significance.

Demographic and other baseline characteristics will be summarized across all randomized subjects.

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 CARAT Statistical Analysis Plan (SAP).

11.2 Efficacy Assessments

Efficacy will be assessed based on IVUS evaluations, lipid profiles, exploratory efficacy biomarkers and exploratory efficacy endpoints.

11.2.1 Primary Efficacy Analysis

The primary endpoint will be a comparison of the primary efficacy parameter between randomized treatment groups (Placebo or CER-001 3 mg/kg) using an analysis of covariance (ANCOVA) with adjustment for baseline PAV. The adjusted mean endpoint in each treatment group and the difference in means (95% confidence interval) will be presented. Statistical significance will be assessed at the alpha=0.05 level. The ANCOVA model will be replaced with non-parametric testing if the normality assumption is violated.

11.2.2 Secondary Efficacy Analysis

The secondary efficacy endpoints will be constructed from a comparison of the secondary efficacy parameters between randomized treatment groups using an analysis of covariance (ANCOVA) with adjustment for the baseline value. The adjusted mean endpoint in each treatment group and the difference in means (95% confidence interval) will be presented. Statistical significance will be assessed at the alpha=0.05 level with no adjustment for multiple
comparisons due to the multiple secondary endpoints. If the normality assumption is violated, nonparametric testing will be used.

### 11.2.3 Exploratory Efficacy Biomarkers

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. Biomarkers will be compared between randomized treatment groups using a t-test if the normality assumption appears reasonable, or a Wilcoxon rank-sum test otherwise, based on the available data. Statistical significance will be assessed at the $\alpha=0.05$ level with no adjustment for multiple comparisons.

### 11.2.4 Exploratory Efficacy Endpoints

Time to first event (TFE) will be evaluated as an exploratory endpoint, given the sample size and short treatment and follow-up duration which render the study underpowered for statistical significance on MACE clinical endpoints (although each endpoint will be reported on descriptively by randomized treatment group). Length of time will be defined as the duration between the date of randomization (RINF1 visit) and the date of the first event of adjudicated cardiovascular death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, fatal stroke, coronary revascularization procedures (PCI, CABG), hospitalization for unstable angina, hospitalization for CHF, any admission for a procedure for the treatment of PVD (including cerebrovascular procedures). Subject will be censored at the date of last contact if there is no documentation of an endpoint event. For subjects who prematurely discontinue the study, their date of last contact will reflect the end of their follow up period.

Time to first event will be graphically represented using Kaplan-Meier survival curves and compared across treatment groups using a log-rank test at the alpha=0.05 significance level.

### 11.3 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.

#### 11.3.1 Safety and Tolerance Variables

Safety and tolerance variables will include:
- Incidence, severity and causality of AEs
- Change from baseline in physical examinations, clinical laboratory tests, vital signs and ECGs
11.3.2 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 also be tabulated by study treatment.

Summary tables will give the number and proportion of subjects 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 SCR and at the FIVUS visits. Shift tables of these values will be provided to summarize the change between SCR and the FIVUS visit for each treatment group.

11.4 Sample Size Calculation

Sample size computation is based on the assumption that the study has 86% power to demonstrate a difference in the change in PAV between the treatment groups of 1.0% with a standard deviation of 2.6%.

This would require 248 subjects with evaluable IVUS imaging at baseline and follow up. To account for an attrition rate of 15%, 146 subjects per group will be randomized per treatment group so that a total of 292 subjects will be randomized in this study.

11.5 Definition of Statistical Significance

All statistical testing will be performed at the $\alpha=0.05$ level of significance.

11.6 Populations for Analysis

The objectives of this study will be addressed with a modified Intention-to-Treat mITT approach. In this approach all randomized subjects with a valid, post randomization efficacy measurement, i.e., a follow up IVUS 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 subject who have received all ten infusions of study drug at the planned dosage and have no major protocol violations.

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

12 ETHICAL CONSIDERATIONS

12.1 Institutional Review Board/Ethics Committee

This protocol and all appropriate amendments will be properly reviewed and approved by an Institutional Review Board (IRB) or Ethics Committee (IEC). Signed and dated notification of the IRB/IEC’s approval must be made to the Sponsor and Investigator prior to study initiation. The Investigator will make required progress reports and report SAEs to the IRB/IEC as per IRB/IEC reporting requirements.

12.2 Ethical Conduct of Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki (Appendix B) and cGCPs (ICH E6) and in compliance with local regulatory requirements and 21 CFR 312. Subject 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 subject identity will remain confidential.

12.3 Subject 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 subject prior to signing the consent form. Prior to the conduct of any screening tests or procedures, the subject 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/ARO and an IRB/IEC. It must contain all the elements in the sample form using language readily understood by the subjects.

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

12.4 Protocol Adherence

The Investigators must read the protocol thoroughly and must follow the instructions exactly. Any deviations must be agreed to by prior discussion between the Sponsor/CRO/ARO and the Investigators, with appropriate written protocol amendments made prior to effecting the agreed upon changes.
Investigators must ensure that any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) is approved by the IRB/IEC before it is implemented.

13 DATA HANDLING AND RECORD KEEPING

13.1 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/ARO’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.

13.2 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 subject 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.

13.3 Source Documentation

The Investigator will keep accurate separate records (other than the CRFs) of all subjects' visits, being sure to include all pertinent study related information. A statement will be made in the subject chart indicating that the subjects have been enrolled in Protocol CER-001-CLIN-010 and the visit dates. Thoroughly document all side effects and AEs in the subject chart. Include results of any diagnostic tests conducted during the study in the source documentation. Record any telephone conversations with the subject and/or Sponsor concerning the study.

13.4 Monitoring, Quality Control and Quality Assurance

The Sponsor/CRO/ARO will be responsible for monitoring the study, data entry and data management. If designated by the Sponsor, the CRO/ARO 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/ARO 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/ARO and the Sponsor's independent Quality Assurance Department or designee. The Investigators will allow CRO/ARO and the Sponsor's representatives and any regulatory agency to examine all study records, CRFs, corresponding subject 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.

13.5 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:
   o 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
   o 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.

14 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.

15 PUBLICATION OF STUDY RESULTS

The CARAT 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.

16 OTHER INFORMATION

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


## APPENDIX A: CARAT PROCEDURES FLOWCHART

<table>
<thead>
<tr>
<th>CARAT PROCEDURES FLOWCHART</th>
<th>SCREENING</th>
<th>BASELINE IVUS (0-7 days)</th>
<th>RINF1 (1-7 days)</th>
<th>INF2 and INF3 (7 +/- 2 days)</th>
<th>INF4 (7 +/- 2 days)</th>
<th>INF5 through INF9 (7 +/- 2 days)</th>
<th>INF10 (7 +/- 2 days)</th>
<th>EOTP³ (7 +/- 2 days)</th>
<th>FINAL IVUS (FIVUS) (14 +/- 7 days)</th>
<th>30 Day FU (SMFU) ( +/- 5 days from EOTP³)</th>
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¹Pre- and peri-menopausal women only ²Pre- and post-infusion ³EOTP visit may be combined with Final IVUS visit if FIVUS visit is performed within 2 weeks of last infusion. ⁴If bloods are out of range at FIVUS visit or at Investigator discretion. ⁵IVUS sent to Core Lab
APPENDIX B: 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 minimises 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 minimise 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 authorised 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 authorised 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.