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

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The primary objectives of the study are:• To evaluate the effect of 24 weeks treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA) as compared to placebo using 3T magnetic resonance imaging (3T-MRI);• To evaluate the safety and tolerability...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac and vascular disorders congenital
Study type	Interventional

Summary

ID

NL-OMON46978

Source
ToetsingOnline

Brief title
TANGO

Condition

- Cardiac and vascular disorders congenital
- Lipid metabolism disorders

Synonym
Low HDL-cholesterol; familial primary hypoalphalipoproteinemia

Research involving
Human

Sponsors and support

Primary sponsor: Cerenis Therapeutics SA
Source(s) of monetary or material Support: Sponsor Cerenis Therapeutics SA

Intervention

Keyword: ApoA-1, CER-001, familial primary hypoalphalipoproteinemia, HDL-c deficiency

Outcome measures

Primary outcome

The primary efficacy parameter of this study will be the change from baseline

after 24 weeks treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA)

as compared to placebo using 3T-MRI when administered to patients with FPHA.

The primary safety parameter will be to evaluate safety and tolerability of

CER-001 administered for 24 weeks.

Secondary outcome

The secondary efficacy parameters will be to evaluate the:

• Change from baseline after 8 week and 48 week treatment with CER-001 on

carotid Mean Vessel Wall Area (MVWA) as compared to placebo using 3T-MRI when

administered to patients with genetically defined FPHA;

• Change from baseline after 8, 24 and 48 week treatment with CER-001 on

femoral artery as compared to placebo using 3T-MRI when administered to patients with genetically defined FPHA;

• Change from baseline at 24 weeks in the target (plaque) to background (blood) ratio (TBR) from an index vessel (either right carotid or left carotid) based on the standardized 18FDG uptake measured with PET/CT in patients with genetically defined FPHA.

The secondary safety parameter will be to:

Evaluate safety and tolerability of CER-001 administered for 48 weeks

Safety parameters will also be evaluated as secondary endpoints and will include:

• Incidence and severity of AEs from routine monitoring;

• Incidence of abnormalities and changes from baseline in clinical laboratory parameters from testing of blood and urine, including anti-ApoA-1antibody;

• Incidence of cardiovascular events.

Exploratory efficacy parameters:

• Changes from Baseline in carotid normalized wall index assessed by 3T-MRI from baseline to week 24 and week 48;

• Changes from baseline to week 24 and week 48 of potential markers on vessel wall biology including and not restricted to laboratory variables such as absolute and relative change in high sensitivity C-reactive protein (hs-CRP), MMP-9 and other selected inflammatory markers (TNFα, IL-6), soluble VCAM-1,

PON-1 and sMCP1, plaque characterization indexes using 3T-MRI;

• Cholesterol efflux capacity after CER-001 administration;

• Changes from baseline of apoA-I level;

• Changes from baseline in total cholesterol, unesterified cholesterol,

esterified cholesterol, triglycerides, apolipoprotein B, apolipoprotein and

lipoprotein profiles for total and unesterified cholesterol by HPLC.

Additional efficacy parameters

• Change form baseline after 72 week treatment with CER-001 on carotid MVWA

using 3T-MRI when administered to patients with genetically defined FPHA

• Change from baseline after 72 week treatment with CER-001 on femoral artery

using 3T-MRI when administered to patients with genetically defined FPHA.

Study description

Background summary

Familial primary hypoalphalipoproteinemia (FPHA) is caused by a genetic defect in one or more of the genes responsible for high-density lipoprotein (HDL) synthesis/maturation, such as ABCA1 and ApoA-I, and is associated with a very low number of HDL particles, also reflected in a very low plasma concentration of ApoA-I.

The major carriers for cholesterol in blood are the lipoproteins, including the low-density lipoprotein (LDL) particles and the HDL particles. In a healthy human body, there is a balance between the delivery and removal of cholesterol. The LDL particles deliver cholesterol to organs, where it can be used to produce hormones, maintain healthy cells, and be transformed into natural products that assist in the digestion of lipids. The HDL particles remove cholesterol from arteries and tissues to transport it back to the liver for storage, recycling, and elimination through a pathway called 'reversed lipid transport' (RLT). Low blood circulation levels of HDL particles leads to an absent or deficient RLT capacity which is insufficient to prevent accumulation

of cholesterol in the peripheral tissues and results in the development of premature cardiovascular disease.

Current management of patients with FPHA is very limited and is focused on diet control and aggressive LDL-cholesterol directed pharmacotherapy that is proven useful adjuncts for managing overall cardiovascular risk. There is no treatment currently available, which can directly restore normal HDL levels/functioning. Studies have consistently shown that decreased HDL-C levels are strongly associated with an increased risk of developing coronary artery disease.

CER-001 is a complex consisting of recombinant human ApoA-I and a proprietary combination of charged phospholipids. It is designed to mimic the action of natural nascent, discoidal pre-beta-HDL 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 tissue and in that way preventing/inhibiting complications due to atherosclerotic diseases.
This phase III study will confirm whether or not administration of CER-001 will be beneficial to patients with FPHA.

Study objective

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

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

The exploratory objectives of the study include:
• Evaluate the effect of treatment with CER-001 with respect to other efficacy measurements including carotid artery and carotid normalized wall index using 3T-MRI;
• Evaluate the effect of treatment with CER-001 with respect to potential surrogate markers on vessel wall biology including laboratory variables;
• Evaluate the effect of treatment with CER-001 with respect to inflammation;
• Evaluate plasma-mediated cellular Cholesterol efflux capacity;

• ApoA-I levels (pharmacokinetic parameters);
• Cholesterols, triglycerides, lipids, apoplipoprotein and lipoprotein levels (pharmacodynamics parameters).

Other objectives of the study include:
• To evaluate the safety and tolerability of 72 week treatment with CER-001.
• To evaluate the effect of 72 week treatment with CER-001 on MVWA using 3T-MRI.
• To evaluate the effect of 72 week treatment with CER-001 on femoral artery using 3T-MRI.

Study design

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

Patients will be randomized to receive treatment with CER-001 or placebo, at a ratio 2:1.
The dose of CER-001 is 8 mg/kg.

The study duration can be 68 -92 weeks in total:
- Screening period: up to 16 weeks (+/-7 days).
- Treatment period: the overall treatment period is up to 48 weeks (+/- 7 days) including an induction treatment phase of 8 weeks, followed by a 16 weeks maintenance treatment phase and a 24 weeks extension treatment phase.
- Safety follow-up period: 4 weeks (+/- 7 days) after the end of treatment (week 52 visit)
OR
- Safety extension follow up: 24 weeks (+/- 7 days) treatment followed by a 4-week (+/- 7 days) follow up period after the end of treatment.

Patients having completed their last infusion 48 weeks after the first one will be offered to continue in the study for 6 months for safety follow up. All patients who accept to continue will be treated with CER-001 8 mg/kg (independent of their treatment in the double blind phase). A total of 12 infusions will be administered bi-weekly until week 72. A final telephone contact will occur at week 76 (4 weeks after the last infusion).

Intervention

The subjects will receive CER-001 (8mg/kg) or placebo via infusion.
During the double blind treatment phase a total amount of 29 doses are given:

weekly during the first 8 weeks (9 doses) and then every two weeks during the following 40 weeks (20 doses).
During the open-label extension phase a total of 12 doses are given: every two weeks during 24 weeks.

During the course of the study:
- 5 times a 3T-MRI is performed (4 times during the double blind treatment phase and once (optional) during the open-label extension phase)
- A 18FDG PET/ CT scan is performed twice.

Study burden and risks

Current management of patients with FPHA is very limited and is focused on diet control and aggressive LDL-C-directed pharmacotherapy that has proven useful adjuncts for managing overall cardiovascular risk. There is no treatment currently available, which can directly restore normal HDL levels/functioning. CER-001 is designed to mimic the actions of natural HDL.

Previous studies have shown that CER-001 is well tolerated in humans. The dose given in this study (8mg/kg) is not expected to lead to major adverse events or laboratory result abnormalities.

CER-001 is administered by infusion. During the course of the study the patient will receive 29 infusions (or 41 if patients participates in the open-label extension phase). The infusion could lead to local injection site reactions and allergic responses. The following symptoms could occur: 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.

Other study related procedures are:
- 3T-MRI at baseline, week 8, week 24, week 48 (and week 72, which is optional).
- PET/CT scan at baseline and week 24.
- 12-lead ECG at screening, baseline, week 4, week 8 and every 8 weeks thereafter (max. 9 times).

Risks involved:
PET/CT scan: radiolabeled 18F-FDG is injected. Generally no side effects are noticed.
ECG: redness or itching caused by sticky pads.

The following procedures are performed at screening, baseline, week 4, week 8 and every 8 weeks thereafter (max. 9 times)
- blood draws for clinical chemistry (including fasting glucose and HbA1c), hematology and coagulation (including pregnancy test at screening).
- urinalysis (including pregnancy test as of baseline).

- physical examination.
- measurement of vital signs and weight.

Additional blooddraws:
- Genotyping at screening.
- FSH at screening (for post-menopausal women only).
- biomarker sample at baseline
- markers for inflammation, oxidation and cardiovascular risk at screening, baseline, week 8, week 24 and week 48.
- lipid & lipoprotein profile at screening, baseline, week 8, week 24 and week 48.
- anti-ApoA-I antibody at screening, week 8, week 24 and week 48.
- PK sampling two hours after infusion at baseline and week 24.

The risks related to blood draws are fainting, redness, bruising, bleeding or infection at the puncture site.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

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

Inclusion criteria:
1. Male and female patients, aged 18 and above.
2. Female patients who are not either surgically sterile (e.g., tubal ligation or removal of ovaries or uterus) or post-menopausal (no spontaneous menstrual periods for at least one year) must agree to use one of the following forms of contraception from screening until 90 days after the completion of the study medication:(1) systemic hormonal treatment (2) an IUD which was implanted at least 2 months prior to screening or (3) "double-barrier" contraception (condom, diaphragm and spermicide are each considered a barrier), or (4) agree to remain sexually abstinent during the entire study period (when contraception is not acceptable for cultural or religious beliefs).
3. Sign written informed consent after the scope and nature of the investigation have been explained to them before screening evaluations and willing to comply with the study restrictions.
4. Are fluent in the language of the investigator, study staff (including raters), and the informed consent.
5. Diagnosis of genetically confirmed HDL-c deficiency due to defects in genes coding for e.g. ABCA1 and/or ApoA -I.
6. IF the subject is on lipid lowering therapy or NEEDS to be treated with lipid lowering therapy then the subject must be on a stable dose at least 6 weeks prior to baseline procedures.
7. Background symptomatic or a-symptomatic cardiovascular disease should been present as such:
- for symptomatic cardiovascular disease: i) history of cardio or cerebrovascular events, ii) diagnosed coronary artery disease (CAD), iii) diagnosed carotid or peripheral stenosism iv) previous myocardial revascularisation- percutaneous coronary intervention (PCI) , or coronary artery bypass graft (CABG).
- for asyptomatic cardiovascular disease: patients with subclinical atherosclerosis diagnosed using imaging method such as i) vDoppler ultrasound, ii) vB-mode ultrasonography-measurement of carotid intima media thickness, iii) v intravascular ultrasonography, iv) Computed Tomography, v) Magnetic Resonance Imaging.
8. ApoA-1 <= 110 mg/dL.
9. HDL cholesterol <= 35 mg/dL or 0.09 mmol/L

Exclusion criteria

Patients meeting any of the following criteria are not eligible for the study:
1. Patient with LCAT mutation will be excluded;
2. Patient who experienced a cardiovascular event within 6 months prior to the onset of screening;
3. Patient who experienced stroke or other cerebrovascular event within 1 year prior to the onset of screening;
4. Patient with triglycerides level above 500 mg/dL;
5. The patient has evidence of clinically significant, uncontrolled or unstable cardiovascular, renal, hepatic (incl. AST or ALT at or above 3x ULN, or bilirubin at or above 2x ULN), gastrointestinal, hematologic, immunological, neurological, endocrine, metabolic or pulmonary disease (as determined by medical history, clinical laboratory or ECG results, or physical examination) or any other medical disorder that would increase the risk associated with taking study medication or would confound the interpretation of study results;
6. Patients with a body mass index (BMI) < 17 kg/m2 or > 40 kg/m2;
7. Patients with severe anemia defined as hemoglobin level below or equal to 10 g/dL;
8. Any clinically significant abnormal laboratory data, vital signs, physical examination at screening or baseline, which in the opinion of the investigator, would interfere with safety assessments;
9. Clinically significant electrocardiogram (ECG) abnormality at screening, including sinus bradycardia (resting heart rate < 50 beats per minute), 2nd or 3rd degree atrioventricular block, prolonged QTc (QTcF >= 450 ms in males and >= 470 ms in females) history of congenital long QT syndromes, or risk of Torsades de Pointes because of family history of sudden death, etc.;
10. Positive result on the serum pregnancy test or are breast feeding at screening, or intend to become pregnant during the course of the trial;
11. Male intending to father a child during the study;
12. Likely to be unreliable as a study participant based on the Investigator's (or designee*s) knowledge of the patient (e.g., alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis);
13. Symptomatic (NYHA Class II or greater) congestive heart failure requiring and persisting despite appropriate medical treatment;
14. Uncontrolled blood pressure: systolic blood pressure >= 160 mmHg and/or diastolic blood pressure >=100 mmHg at screening or any other pre-randomization visit;
15. Uncontrolled diabetes mellitus defined as HbA1c >10%;
16. Unexplained creatine phosphokinase level > 3 times the ULN;
17. History of malignancy during the 3 years prior to screening, with the exception of basal cell carcinoma of the skin;
18. Current alcohol or drug abuse or history thereof within 5 years prior to screening
19. Contraindication to MRI scanning such as imbedded metal (e.g., schrapnel), implanted metal objects (e.g., pacemaker), claustrophobia;
20. Participated in any investigational study or taken an investigational drug within 30 days (or 5 times the half-life of the investigational drug, whatever is longer);
21. Ever received CER-001within 6 month from the onset of screening;
22. Medically non-compliant in the management of their disease in the investigator*s opinion.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-12-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Recombinant Human ApolipoproteinA-1/Phospholipids Complex
Generic name:	Recombinant Human ApolipoproteinA-1/Phospholipids Complex

Ethics review

Approved WMO Date:	28-09-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2015
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-003713-23-NL
CCMO	NL54942.018.15

Study results

Results posted: 12-12-2019

Summary results
Trial ended prematurely

First publication
05-12-2019