S Y N O P S I S

Study title	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
Investigational product	CER-001
Indication studied	GENETICALLY DEFINED HYPOALPHALIPOPROTEINEMIA
Study code (if applicable)	TANGO
Coordinator or Investigator	Pr Eric STROES
Number of study centres	19 opened sites
Publication (if applicable)	UNKNOWN
Study period	From 4 DEC 2015 (First patient consent form signature) to 21 DEC 18 (Last patient last visit)
Phase of development	III
Objectives	
Primary	The primary objectives were to evaluate: • The effect of 24-week treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA) as compared to placebo using 3T magnetic resonance imaging (3T-MRI); • The safety and tolerability of CER-001 administered for 24 weeks.
Secondary	The secondary objectives were to evaluate: • The effect of 8-week and 48-week treatment with CER-001 on MVWA as compared to placebo using 3T-MRI; • The effect of 8-week, 24-week and 48-week treatment with CER-001 on femoral artery as compared to placebo using 3T-MRI; • The effect of 24-week treatment with CER-001 in the target (plaque) to background (blood) ratio (TBR) from an index vessel (either right carotid, left carotid) based on the standardized 18FDG uptake measured with PET/CT; • Safety and tolerability of CER-001 administered for 48 weeks
Other	The other objectives were to evaluate: • The safety and tolerability of 72-week treatment with CER-001; • The effect of 72-week treatment with CER-001 on MVWA using 3T-MRI; • The effect of 72-week treatment with CER-001 on femoral artery using 3T-MRI.

Methodology	This was a multicenter, international, double-blind, placebo-controlled, randomized (2 :1), phase III study to evaluate efficacy and safety of CER-001 on vessel wall area in patients with genetically defined familial primary hypoalphalipoproteinemia (FPHA – mutation in ApoA1 and/or ABCA1 gene), receiving background optimized lipid therapy AND with cardiovascular disease. Enrolled patient received 29 infusions of CER-001 or placebo over the 48 week double-blind treatment phase and then 12 infusions of CER-001, during the 24 week open-labeled treatment phase following the last dose administered during double-blind treatment period.
Number of patients	30 patients randomized and 28 patients analyzed in the mITT population.
Inclusion and exclusion criteria	**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-1 6. IF the subject is on lipid-lowering therapy or NEEDS to be treated with lipid-lowering therapy then the subject must be on a stable dose at least 6 weeks prior to the baseline procedures. 7. Background symptomatic or asymptomatic cardiovascular disease should be present as such: - For symptomatic cardiovascular disease: i) history of cardio or cerebrovascular events, ii) diagnosed coronary artery disease (CAD), iii) diagnosed carotid or peripheral stenosis, iv) previous myocardial revascularization - percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG). - For asymptomatic cardiovascular disease: patients with subclinical atherosclerosis diagnosed using imaging method

	such as i) Doppler ultrasound, ii) B-mode ultrasonography – measurement of carotid intima media thickness, iii) intravascular ultrasonography, iv) Computed Tomography, v) Magnetic Resonance Imaging 8. ApoA-1 ≤ 110 mg/dL 9. HDL-cholesterol ≤ 35 mg/dL or 0.9 mmol/L **Exclusion criteria:** 1. Patient with LCAT mutation 2. Patient who experienced a cardiovascular event within 6 months prior to the start of screening 3. Patient who experienced stroke or other cerebrovascular event within 1 year prior to the onset of screening 4. Patients with triglycerides level above 500 mg/dL 5. The patient has evidence of clinically significant, uncontrolled or unstable cardiovascular, renal, hepatic (incl. AST or ALT at or above 3x ULN, or bilirubin at or above 2x ULN), gastrointestinal, hematologic, immunological, neurological, endocrine, metabolic or pulmonary disease (as determined by medical history, clinical laboratory or ECG results, or physical examination) or any other medical disorder that would increase the risk associated with taking study medication or would confound the interpretation of study results. 6. Patients with a body mass index (BMI) < 17 kg/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 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., shrapnel), implanted metal objects (e.g., pacemaker), claustrophobia 20. Participated in any investigational study or taken an investigational drug within 30 days (or 5 times the half-life of the investigational drug, whatever is longer) 21. Ever received CER-001 within 6 months before the start of screening 22. Medically non-compliant in the management of their disease in the investigator's opinion
Study treatment	During the double-blind treatment phase, 8 mg/kg dose of CER-001 or placebo (standard 250 mL sodium chloride solution) was administered as a weekly infusion during the first 8 weeks (9 doses) and then every two weeks during the following 40 weeks (20 doses). During the open-labeled treatment phase 8 mg/kg dose of CER-001 was administered every two weeks during 24 weeks (12 doses). <u>Following CER001 batchs were used in the study:</u> S164/CER001/FC008 exp. 19 /07 /2016 (For The Netherlands only) S218/CER001/FC003 exp. 11/2018 (For The Netherlands only) S218/CER001/FC004 exp. 12/2018 S218/CER001/FC005-A exp. 12/2019 (For The Netherlands only) S218/CER001/FC005-B exp. 12/2019 S218/CER001/FC005-C exp. 12/2019 (For The Netherlands only) S218/CER001/FC005-D exp. 12/2019 S218/CER001/FC006-A exp. 01/2020 S218/CER001/FC007-A exp. 01/2020
Reference treatment (placebo arm)	250 mL of 0.9% sodium chloride injection, USP (or equivalent ex-US) alone was used for the placebo arm. <u>Following NaCl batches labelled and distributed by Catalent to the sites:</u> 15I30G60 exp. 08/2017 15I29G60 exp. 08/2017 17G02G60 exp. 06/2019 18C22G60 exp. 02/2020

Duration of treatment	48 weeks of double-blind treatment phase followed by optional 24 weeks of open-labeled treatment phase.
Primary and secondary endpoints	
Efficacy	The primary efficacy parameter of this study was the change from baseline after 24 weeks treatment with CER-001 on carotid Mean Vessel Wall Area (MVWA) as compared to placebo using 3T-MRI when administered to patients with genetically defined FPHA. **<u>Secondary efficacy parameters were:</u>** • Change from baseline after 8-week and 48-week treatment with CER-001 on MVWA as compared to placebo using 3T-MRI when administered to patients with genetically defined FPHA. • Change from baseline after 8, 24 and 48 weeks treatment with CER-001 on femoral artery as compared to placebo using 3T-MRI when administered to patients with genetically defined FPHA. • Change from baseline at 24 weeks in the TBR from an index vessel (either right carotid or left carotid) based on the standardized 18FDG uptake measured with PET/CT in patients with genetically defined FPHA **<u>Exploratory efficacy parameters were:</u>** • Effect of treatment with CER-001 in patients with genetically defined Familial Primary Hypoalphalipoproteinemia (FPHA) with respect to other efficacy measurements including carotid artery and carotid normalized wall index using 3T-MRI • Effect of treatment with CER-001 in patients with genetically defined Familial Primary Hypoalphalipoproteinemia (FPHA) with respect to potential markers on vessel wall biology including and not restricted to laboratory variables such as absolute and relative change in high sensitivity C-reactive protein (hs-CRP), MMP-9 and other selected inflammatory markers (TNFα, IL-6), PON-1, soluble VCAM-1 and sMCP1, plaque characterization indexes using 3T-MRI • Plasma-mediated cellular Cholesterol efflux capacity. **<u>Other efficacy parameters were:</u>** • Change from 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
Safety	**<u>The primary safety parameter was:</u>** • Safety and tolerability of CER-001 administered for 24 weeks

	Secondary safety parameter were: • Safety and tolerability of CER-001 administered for 48 weeks • Incidence and severity of AEs from routine monitoring. • Incidence of abnormalities and changes from baseline in clinical laboratory parameters from testing of blood and urine, including anti-ApoA-1 antibody. Incidence of cardiovascular events. **Other safety parameters were:** • Safety and tolerability of CER-001 administered for 72 weeks
Other (if applicable)	Not applicable
Procedures (if applicable)	Not applicable
Sample size	The assumptions, upon which the power calculation are based, are data from the 7 patients completing the CER-001-CLIN-007 SAMBA study, given the similarity of the genetic mutations. Those patients presented with a median value for MVWA of 25.0 mm2 and had a follow-up median value at 6 months of 21.8 mm2. The mean percent reduction is reported as 6.7%, standard deviation = 4.5%. These observed values would provide a conservative estimate of the effect of CER-001 in the more severe population for this FPHA study. Using these results from SAMBA (i.e. an assumed standard deviation of 4.5%) and a 2:1 randomization scheme to maximize exposure to active drug, 16 completing patients in the CER-001 group and 8 in the placebo group (24 total completers for mITT) would yield 90% power to detect a difference from baseline versus placebo of 6.7%, using two-tailed testing with α=0.05. A total of 30 patients are planned to be randomized that would provide a buffer such that a 20% discontinuation rate would still allow the study to retain sufficient power for a supporting per protocol efficacy analysis (MVWA).
Statistical methods	The statistical analysis is based on three populations: <u>Safety population</u> The safety population comprised all randomized patients who received at least one dose of study medication and safety analysis was performed on the safety population according to the actual treatment received. <u>Modified Intent-To-Treat (mITT) population</u> The mITT population is comprise all randomized patients for whom at least one of the following conditions is satisfied: • 3T-MRI assessment available at baseline (W0) and at least one post-baseline 3T-MRI assessment available • 18FDG-PET/CT assessment available at baseline (W0) and at least one post-baseline 18FDG-PET/CT assessment available

	Per Protocol (PP) population The PP population will comprise all patients of the mITT population without any major protocol deviations. Analysis of the primary endpoint consist of a main analysis (a linear mixed model with repeated measures), a supportive analysis and several sensitivity analyses
Summary / Conclusions	
Population:	53 patients consented to participate in the study; 23 patients were screen-failed and 30 patients were randomized. 8 patients prematurely discontinued the study: 1 for patient decision, 4 for investigator's decision due to safety reason and 3 for sponsor's decision. 30 patients are included in the safety population. 28 patients are included in the mITT population. 27 patients are included in the PP population.
Baseline characteristics:	30 patients were randomized in a 2:1 ratio between study treatments groups CER-001 and Placebo, respectively. Randomised patients were mainly male (63.3%) with a mean age (SD) of 52.66 (7.39) years (range 34.5 to 65.7). The race and ethnicity was only reported for 36.7% and 26.7%, respectively. For the other patients the data were not deemed collectible due to local regulation on data privacy. All randomised patients presented asymptomatic (n=13, 43.3%) or symptomatic (n=17, 56.7%) cardiovascular disease. The patients randomized in the CER-001 group were more likely to present symptomatic vascular disease (70.0% vs 30.0%). Regarding the details of the symptomatic cardiovascular diagnosed carotid or peripheral stenosis were only reported in the CER-001 group. The other symptomatic events were reported in both groups, however previous myocardial revascularization was more common in the CER-001 group (57.1% vs 33.3%). Nineteen (63.3%) and 28 patients (93.3%) randomised in the study presented at least one medical history or one concomitant disease, respectively. The main medical history other than cardiovascular event were surgical or medical procedure. Nevertheless, regarding the 14 patients reporting history of surgical procedures it mainly included 10 cardiac related events and 3 cardiac related events in the CER-001 and the placebo group, respectively. Regarding concomitant diseases, 6 patients and 3 patients presented congenital familial and genetic disorders in the CER-001 and placebo groups, respectively. It notably consisted in 5 and 1

	Tangier diseases, respectively. One Familial High Density Lipoprotein Deficiency and one Gilbert's Syndrome in each group. Four patients in each group presented metabolism and nutrition disorder mainly consisting in lipid metabolism disorder. Finally, 4 and 3 patients presented nervous system disorders in each group respectively, including 1 carotid arteriosclerosis, 1 cerebrovascular accident and 1 transient ischaemic attack in the CER-001 group. All patients received at least 1 concomitant medication. No noticeable difference was observed between groups regarding the type of treatments received.
Efficacy results:	A linear mixed-effect model was used for the analysis of this primary outcome. Nevertheless, despite a tendency regarding W24 visit and CER-001 treatment, no significant association was evidenced regarding the effect of CER-001 on carotid artery MVWA within 24 weeks of treatment (parameter estimate = -1.46; P-value = 0.051). Subsequently, no effect of the treatment was observed whatever the time point to be analysed nor the mutation of interest. Considering the fact that the primary endpoint was not met, the sponsor decided to not pursue the secondary, exploratory, and other objectives analysis.
Safety results:	Almost all patients (93.3%, n=28) reported at least one treatment emergent adverse event, which is not unusual for a study of this length, including 19 patients (95%) of the CER-001 group and 9 patients (90%) of the placebo group. No fatal AEs were reported during the study. Five serious and severe treatment emergent adverse events (TEAEs) and 2 non-serious severe TEAEs were reported only in the CER-001 group (4 patients (20.0%) presented serious TEAEs and 5 patients (25.0%) presented TEAEs considered as severe). Among these 7 severe events, only an anaphylactic reaction, a hypersensitivity and an unstable angina were considered at least possibly related to CER-001. Permanent study medication discontinuation due to TEAE related to study treatment (as per investigator judgment) was only reported in the CER-001 group (n=4, 20.0%). These related events were: 2 severe SAEs (anaphylactic reaction and unstable angina), 1 severe non-serious AE (hypersensitivity) plus 2 mild non-serious AEs (pruritus and rash).

	Regarding the other parameters, abnormal clinically laboratory values were rare. Only one patient in each group had abnormal and clinically significant results reported. For the patient treated in the CER-001 group, the corresponding reported AEs were assessed as moderate and not related to the study treatment. Considering ECG results analysis, all patients presented normal or abnormal and not clinically significant ECG results at baseline and W0. Moreover, through the different visits of the study the ECG results remained quite similar in each group.
Other:	Not Applicable
Conclusion	This study did not permit to confirm the efficacy signal reported in both MODE and SAMBA studies. Nevertheless, even if the analysis of the primary criterion did not reach significance, a trend in association between treatment and week 24 was observed. It suggests that an effect could be evidenced in advanced FH patients. Nevertheless, the design of the study and especially the sample size did not enable us to observe the effect of CER-001. Safety data were consistent with previous studies considering the length of the treatment and the severity of the underlying pathology. Hence, with regard to benefit/risk profile, CER-001 still represents a potential treatment for patients with abnormal lipoprotein profile and warrant further clinical studies.