Press Release

Cerenis Therapeutics announces the results of the LOCATION study

The LOCATION study demonstrates the functionality of CER-001 in increasing cholesterol efflux capacity and targeting plaques in patients with advanced atherosclerotic disease

Toulouse, FRANCE, Ann Arbor, UNITED STATES, July 15, 2015 – **Cerenis Therapeutics (FR0012616852 - CEREN),** an international biopharmaceutical company dedicated to the discovery and development of innovative HDL therapies ("good cholesterol") for treating cardiovascular and metabolic diseases, today announced the results of the LOCATION clinical study, which evaluated the selectivity of CER-001, an HDL mimetic made of recombinant human apolipoprotein A-I (apoA-I) and phospholipids, for carotid plaques in patients with advanced atherosclerotic disease.

The LOCATION study provides the first evidence of CER-001 selective targeting of atherosclerotic plaques in patients, and of the role of plaque permeability in plaque penetration by an HDL mimetic. The study evaluated 8 patients with >50% atherosclerotic stenosis of the carotid artery who received an infusion of CER-001 (3 mg/kg body weight) labeled with Zirconium-89, a tracer suited for PET/CT imaging, to determine the extent to which CER-001 targets and penetrates atherosclerotic plaques and the effect on cholesterol efflux, a marker which is inversely related to the incidence of adverse cardiovascular events[1].

- ### CER-001 penetrates atherosclerotic plaques

Using serial PET/CT imaging, the investigators were able to show that plaque uptake of CER-001 increased significantly 24 hours after infusion (14%), and remained increased up to 48 hours (12%). This is the first demonstration of plaque penetration by CER-001 in patients with atherosclerotic disease.

- ### CER-001 preferentially targets atherosclerotic plaques

By looking at specific segments of the carotid arteries with and without atherosclerotic plaques, the investigators were able to show that the uptake of CER-001 was higher in segments with plaques than in non-plaque segments demonstrating that infused CER-001 preferentially enters atherosclerotic plaques in patients. Using an imaging technique that allows the evaluation of the permeability of atherosclerotic plaques, they were also able to show that the extent to which CER-001 enters the plaque is determined by the plaque's permeability. This observation supports the concept and may be particularly relevant for the selection of patients most likely to benefit from apoA-I-containing HDL-mimetic therapy based on plaque permeability.

- ### CER-001 increases cholesterol efflux capacity

In addition, by collecting serial blood samples, the investigators showed that one hour after CER-001 infusion plasma-mediated cholesterol efflux increased by 13.8% and mean plasma apoA-I levels increased by 9.9 mg/dL. Both apoA-I levels and cholesterol efflux capacity returned to baseline values after 24 hours.

The results of the LOCATION study are consistent with the findings of the CER-001 clincial program to date, which have shown that CER-001 effectively mobilises cholesterol and regress atherosclerosis. The findings validate plaques targeting with CER-001 at the dose being investigated in the planned CARAT study (NCT02484378), a double-blind, placebo-controlled, phase II study assessing the effect of CER-001 on atherosclerosis regression in patients with acute coronary syndrome (ACS).

Professor Erik Stroes, Principal Investigator of the LOCATION study commented that: "*The LOCATION study confirms for the first time the targeting of atherosclerotic plaques by apoA-I containing HDL mimetics in humans, an effect only previously observed in experimental models of atherosclerotic disease. Targeting of atherosclerotic plaques was observed at a dose of 3 mg/kg, the dose that will be used in the Phase II CARAT clinical trial in post-ACS patients the first of whom will be enrolled into the trial this quarter. Encouragingly, the LOCATION study has also shown that CER-001 targeting of atherosclerotic plaques is associated with an increased cholesterol efflux capacity, a marker that was recently demonstrated by Daniel J. Rader and his team at University of Pennsylvania to be predictive of a reduction in cardiovascular-related mobidity and mortality. Our results are also consistent with the observed reduction in atherosclerosis shown in patients with HDL deficiencies, in patients with homozygous familial hypercholesterolemia, and in post-ACS patients. We will be submitting the full results from the LOCATION study to a peer-reviewed journal shortly*".

Dr. Jean-Louis Dasseux, Founder and CEO of Cerenis Therapeutics commented*: "The findings of the LOCATION study offer valuable insights for apoA-I HDL mimetic infusion therapies, and may help guide future strategies using HDL mimetics to target plaques directly. The results confirm that CER-001 behaves as a true natural pre-beta HDL by targeting the atherosclerotic plaques. They provide further evidence to support the continued clinical development of CER-001 in patients with HDL deficiencies, indications for which we have received two orphan drug designations in apoA-I and ABCA1 deficiencies, and for promoting plaque regression in post-ACS patients"* .

Reference

1. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, Neeland IJ, Yuhanna IS, Rader DR, de Lemos JA, Shaul PW. HDL Cholesterol Efflux Capacity and Incident Cardiovascular Events. *N Engl J Med*. 2014;371(25):141118051511004.

Notes to editors

Atherosclerosis is a disease arising from formation of plaques, so-called atherosclerotic plaques, caused by deposits of lipids, especially cholesterol, in the vessel wall, which leads to the manifestation of cardiovascular diseases including myocardial infarction ("heart attack") and angina pectoris all designated by the term acute coronary syndrome (ACS). Atherosclerosis affects the entire vascular system and also leads to several other complications, including ischaemic stroke, renal failure and arteriopathy of the lower limbs.

The major carriers for cholesterol in the blood are lipoproteins, including the low-density lipoprotein (or LDL) particles, and the high-density lipoprotein (or HDL) particles. In a healthy human body, there is a balance between the delivery and removal of cholesterol. The LDL particles deliver cholesterol to organs, where it can be used to produce hormones, maintain healthy cells, and be transformed into natural products that assist in the digestion of lipids. The HDL particles remove cholesterol from arteries and tissues to transport it back to the liver for storage, recycling, and elimination through a pathway called "Reverse Lipid Transport (RLT)".

Epidemiological studies have historically demonstrated that the risk of developing cardiovascular disease appeared to be higher in patients with low HDL-cholesterol independent of the level of LDL-cholesterol, even when patients are treated with the best available standard of care. This observation can be explained by the role the HDL particle plays in the Reverse Lipid Transport (RLT) pathway, the only natural mechanism capable of removing cholesterol from peripheral tissues and delivering it back to the liver for elimination. HDL particles mediate the flux of cholesterol through the RLT and therefore act to counterbalance the delivery of cholesterol to the vessel wall by the LDL particles. The RLT is a pathway that may protect against atherosclerosis and cardiovascular disease by clearing excess cholesterol from the arterial wall. The ATP-binding cassette transporter called ABCA1 is a protein that mediates the first step of RLT and acts as a gatekeeper for eliminating excess tissue cholesterol.

About Cerenis Therapeutics: www.cerenis.com

Cerenis Therapeutics is an international biopharmaceutical company dedicated to the discovery and development of innovative HDL therapies for the treatment of cardiovascular and metabolic diseases. HDL is the primary mediator of the reverse lipid transport, or RLT, the only natural pathway by which excess cholesterol is removed from arteries and is transported to the liver for elimination from the body.

Cerenis is developing a portfolio of HDL therapies, including HDL mimetics for the rapid regression of atherosclerotic plaques in high-risk patients such as post-ACS patients and patients with HDL deficiency, and drugs which increase HDL for patients with low number of HDL particles to treat atherosclerosis and associated metabolic diseases.

Cerenis is well-positioned to become one of the leaders in the HDL therapeutic market, with a broad portfolio of programs being developed.

Since its inception in 2005, the company has been funded by top tier investors: Sofinnova Partners, HealthCap, Alta Partners, EDF Ventures, Daiwa Corporate Investment, TVM Capital, Orbimed, IRDI/IXO Private Equity and Bpifrance (Fund for Strategic Investment) and last March successfully completed an IPO on Euronext Paris raising €53.4m.

About CER-001:

CER-001 is an engineered complex of recombinant human apoA-I, the major structural protein of HDL, and phospholipids. It has been designed to mimic the structure and function of natural, nascent HDL, also known as pre-beta HDL. Its mechanism of action is to increase apoA-I and the number of HDL particles transiently, to stimulate the removal of excess cholesterol and other lipids from tissues including the arterial wall and to transport them to the liver for elimination through a process called Reverse Lipid Transport.

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