Press Release

First patient enters Phase III TANGO clinical trial to evaluate efficacy to regress atherosclerosis and safety of CER-001 in patients with Familial Primary HypoAlphalipoproteinemia (FPHA)

- **A trial headed by Prof. Erik Stroes, Professor of Medicine, Head of the Department of Vascular Medicine at the Academic Medical Center in Amsterdam, The Netherlands**

- **The primary objective of the TANGO trial is to evaluate the effect of 24 weeks treatment with CER-001 on carotid vessel wall area as compared to placebo using magnetic resonance imaging (MRI)**

Toulouse, FRANCE, Ann Arbor, UNITED-STATES, December 10, 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 announces that the first patient has been enrolled into the Phase III TANGO trial that is designed to assess both the efficacy of CER-001 to regress atherosclerosis and its safety in patients with FPHA, who are characterized by ABCA1 or apoA-I genetic mutation and receiving background optimized lipid therapy.

Inherited defects in the apoA-I or ABCA1 genes can act in a dominant manner to cause FPHA, a rare syndrome characterized by the absence or severe deficiency of HDL particles in the circulation. This means that the the body's only natural mechanism for the elimination of cholesterol is compromised. These patients experience a rapid accumulation of cholesterol, particularly in blood vessels, which often results in accelerated atherosclerosis and premature cardiovascular disease.

The TANGO trial, which began in the 4th quarter of 2015 as announced to investors at the time of the Company's IPO, is on schedule and results are expected in Q3 2017.

- **A trial headed by Professor Erik Stroes, Professor of Medicine, Head of the Department of Vascular Medicine at the Academic Medical Center in Amsterdam, The Netherlands**

The TANGO trial is a multicenter, randomized, 48-week, double-blind, parallel-group, placebo-controlled study involving thirty patients from several sites across Europe, Canada, the United States and other countries based on availability of patients with this rare orphan disease.

The TANGO Steering Committee includes, **Prof. Erik Stroes**, MD, PhD, Professor of Medicine, Head of the Department of Vascular Medicine at the Academic Medical Center in Amsterdam, The Netherlands; **Prof. Jacques Genest**, MD, Department of Medicine, Division of Cardiology, Faculty of Medicine, McGill University, Montréal, Canada; **Prof. Henry Ginsberg**, MD, Irving Professor of Medicine at Columbia University College of Physicians and Surgeons, New York, NY, USA; **Prof. Eran Leitersdorf**, Director, Center for Research, Prevention and Treatment of Atherosclerosis, Professor of Medicine Dorothy & Maurice Bucksbaum Chair in Molecular Genetics and Dean of the Hebrew University of Hadassah School of Medicine, Israel; **Prof. Arnold von Eckardstein**, Chair of the Institute of Clinical Chemistry at the University of Zurich, Switzerland, Professor of Clinical Chemistry at the University of Zurich and Director of the Institute of Clinical Chemistry of the University Hospital of Zurich, Chairman of the European Lipoprotein Club and Chairman of the Executive Committee of the Swiss Working Group on Lipids and Atherosclerosis. He is the past President of the German Society of Arteriosclerosis Research and of the Swiss Society of Clinical Chemistry. Former vice-president of International Task Force for the Prevention of Coronary Heart Disease; **Prof. Paolo Raggi**, Professor of Medicine, University of Alberta, Edmonton, Canada and Academic Director of the Mazankowski Alberta Heart Institute and Section Chief, Cardiology, at Alberta Health Services in 2012. He also serves as Chair of Cardiac Research.

Prof. Erik Stroes, Professor of Medicine, Head of the Department of Vascular Medicine at the Academic Medical Center in Amsterdam, The Netherlands, and Principal Investigator of the TANGO trial, commented, *"In the LOCATION and SAMBA clinical studies, we have observed that CER-001 preferentially targets atherosclerotic plaques and stimulates cholesterol removal by emulating all the steps of the reverse cholesterol transport pathway. This increased lipid removal has been accompanied by marked reductions in atherosclerosis as measured by the reduction in the vessel wall dimensions of atherosclerotic arteries in patients with genetically-determined low HDL cholesterol. The TANGO trial aims to give us more data on the use of CER-001 for chronic administration in patients with a high unmet clinical need."*

- **The primary objective of the TANGO trial is to evaluate the effect of 24 weeks treatment with CER-001 on carotid vessel wall area as compared to placebo using magnetic resonance imaging (MRI)**

The primary objective of the TANGO trial is to evaluate the effect of 24 weeks treatment with CER-001 on carotid vessel wall area as compared to placebo using magnetic resonance imaging (MRI). Cerenis Therapeutics has received two Orphan Drug Designations from the European Medicines Agency (EMA) for the use of CER-001 in the treatment of patients with apoA-I and ABCA1 deficiencies, the two patient populations who will be recruited into the TANGO trial. Prior data supporting the orphan designation applications were obtained from the SAMBA Phase II trial of CER-001 in patients with FPHA which showed that CER-001 reconstituted the reverse lipid transport (RLT) pathway in individuals who have defects in the natural HDL pathway, facilitating elimination of cholesterol from the body. Importantly, one month of treatment with 9 doses of CER-001, provided on top of optimized standard of care for LDL-C-lowering therapy, resulted in a statistically significant reduction in carotid artery mean vessel wall area, as measured by magnetic resonance imaging.

Dr. Samia Mora, Associate Professor of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, USA commented, *"These patients accumulate cholesterol and experience premature cardiovascular events despite essentially 'normal' levels of LDL-C or despite having been placed on optimized statin therapy. The mechanism of action of statins does not directly target this pathophysiology in these patients with FPHA and there is no treatment currently available that can directly restore normal HDL function or normal levels of apoA-I. Despite receiving the best standard of care, many patients have a persistent and high risk of adverse cardiovascular events and premature death, underscoring the unmet medical need for novel therapies. In this regards, the TANGO trial is an important study as it will test in a randomized double-blind placebo-controlled trial whether CER-001 will be a potential new therapeutic strategy for reversing atherosclerosis on top of currently available lipid-lowering agents to address this elevated residual cardiovascular risk and high unmet medical need in this patient population."*

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Notes to editors

What is Familial Primary HypoAlphalipoproteinemia?

Hypoalphalipoproteinemia ("low HDL"), as a general term, has historically been defined clinically as an HDL-cholesterol (HDL-C) less than 40 mg/dL (1.0 mmol/L) in men, and less than 50 mg/dL (1.3 mmol/L) in women. A number of etiologies, often metabolic, can underlie a reduced circulating level of cholesterol in the HDL fraction, for example diabetes, Metabolic Syndrome, obesity, and lack of physical activity (thus called secondary hypoalphalipoproteinemia). In a very small percentage of the population, particularly amongst the patients with the very lowest HDL-C values, there are patients who have a genetic defect (thus called primary hypoalphalipoproteinemia) affecting either the constituent components of the pre-β particle, the process of pre-β particle synthesis, the steps leading to maturation into an alpha HDL particle, or the rates of catabolism – any of which alone or in combination can then result in an inherited condition of very low circulating HDL particle number.

Familial Primary Hypoalphalipoproteinemia (FPHA) includes patients with a range of individual mutations across the key genes involved in HDL particle production or maturation (apoA-I, ABCA1, LCAT) which are individually extremely rare (prevalence less than one in one million births in the homozygous form) but in both homozygous and heterozygous forms can act in an autosomal dominant manner to cause low apoA-I levels and low HDL particle numbers through either decreased production or increased clearance and premature destruction of HDL particles and ultimately result in accelerated atherosclerosis from a single final common pathophysiology of impaired Reverse Lipid Transport (RLT) and accumulation of cholesterol throughout the body, in particular, the vasculature. FPHA patients are at high risk of cardiovascular disease as a consequence of having inherited a virtually absent endogenous RLT system. Because of the specific characteristics and very limited available therapeutic approaches, FPHA remains an unmet medical need and a life-threatening condition.

How is the TANGO trial designed?

TANGO is a Phase III, multicenter, randomized, 48-week, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of CER-001 on vessel wall area in thirty patients with genetically defined familial hypoalphalipoproteinemia (apoA-I and ABCA1 deficiencies) and receiving background optimized lipid therapy. Primary endpoint: to evaluate the effect of 24 weeks' treatment with CER-001 on carotid mean vessel wall area (MVWA) compared with placebo using 3TMRI. Secondary endpoints: : to evaluate the effect of 8 and 48 weeks' treatment with CER-001 on carotid MVWA compared with placebo using 3TMRI, : to evaluate the effect of 8, 24 and 48 weeks' treatment with CER-001 on femoral MVWA compared with placebo using 3TMRI, and to evaluate the effect of 8, 24 and 48 weeks' treatment with CER-001 on the change from baseline 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.

What is atherosclerosis?

Atherosclerosis is a disease arising from formation of plaque, so-called atherosclerotic plaque, 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 that are 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 (LDL) particles, and the high-density lipoprotein (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 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 plaque 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 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. Previous Phase II studies have provided important data demonstrating the efficacy of CER-001 in regressing atherosclerosis in several distinct vascular beds in patients representing the entire spectrum of cholesterol homeostasis. The totality of the data to date indicates that CER-001 performs all of the functions of natural pre-beta HDL particles and has the potential to be the best-in-class HDL mimetic in the market.

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