Press release

First results of TARGET PHASE II study demonstrate the ability of CER-001, an HDL mimetic, to target tumor in patients with esophageal cancer

- **Primary objective met: clinically meaningful targeting of esophageal tumor tissue by labeled CER-001**
- **The sustained tumor labeling supports future use of HDL mimetics to improve effective delivery of therapeutic agents**
- **Results are consistent with preclinical studies using HDL mimetics**
- **These encouraging results were observed in patients with esophageal cancer, often refractory to standard therapy**
- **No safety or tolerability issues were observed**

Toulouse, FRANCE, Lakeland, UNITED-STATES, June 25, 2018, 6.00 pm CEST – **Cerenis Therapeutics (FR0012616852 – CEREN – PEA PME eligible)**, an international biopharmaceutical company dedicated to the discovery and development of HDL-based innovative therapies for treating cardiovascular, metabolic diseases, and HDL platform technologies today announced that enrollment of all patients (ten) in TARGET study has been completed on schedule. The preliminary results in five patients are also now available.

- The preliminary data analysis of TARGET demonstrates the ability of a radioactive labeled HDL mimetic (CER-001) to target tumor in patients with esophageal cancer as demonstrated visually and resulted in a calculated 50% signal increase in the tumor after 24h and 72h compared with 1h.
- The sustained radioactive labeling of the tumor, seen in all 5 patients analyzed, was observed over the last two predefined post-dose time points (24h to 72h), and supports using HDL mimetics to improve effective targeted delivery of therapeutic agents.
- These results are encouraging knowing that esophageal cancer is often refractory to the standard of care for this devastating condition.

Full results will be communicated and presented at future medical conferences. Given the uniformly favorable findings seen in *all* 5 patients, the final analysis results are not expected to differ from this preliminary analysis.

TARGET is the first clinical study ever performed to assess labeled HDL tumor uptake in cancer patients and in doing so, the first clinical study to test the ability of HDL to target tumor in patients after interacting with cellular HDL receptors.

In TARGET, CER-001, a pre-beta HDL mimetic, is labeled with Zirconium-89 for serial PET/CT[1] imaging in patients. It has been demonstrated that CER-001 has the same structure and function as a natural

[1] *PECT/CT: **Positron emission tomography–computed tomography** (better known as **PET-CT** or **PET/CT**) is a nuclear medicine technique which combines, in a single gantry, a positron emission tomography (PET) scanner and an x-ray computed*

pre-beta HDL and therefore could be used as a tumor imaging product to target tumors via HDL receptors. A number of preclinical studies have already validated the concept[2, 3], showing that HDL nanoparticles can act as a specific drug delivery platform targeting tumor cells or targeting immune cells.

Cerenis' CER-001 is a recombinant human apoA-I pre-beta HDL mimetic. CER-001 has been shown to be safe and well tolerated in multiple previous clinical trials with more than 5,000 administrations among the different studies and with repeated administrations of up to 18 months. CER-001 is currently in a phase III clinical trial for patients with a genetic HDL deficiency ("TANGO").

The TARGET study is an investigator initiated single-center observational trial enrolling adult subjects with a pathologically proven diagnosis of primary esophageal carcinoma in situ. Patients were all at least T2 staged according to the TNM classification[4]. The investigators planned to include 10 patients, all of whom have now been enrolled.

The two principal investigators of the TARGET study are Professor Dr. Erik Stroes, MD, PhD, Professor and Chair of the Department of Vascular Medicine, Amsterdam Medical Center (AMC) and Professor Dr. Hanneke Van Laarhoven, MD, PhD, Department of Medical Oncology, Amsterdam Medical Center (AMC).

Dr. Jean-Louis Dasseux, Founder and CEO of Cerenis, comments: "These preliminary data support our HDL drug delivery platform based on apoA-I, Cargomer™ and HDL mimetics. It is an important milestone which helps position the company as a leader in the field, as we are the first company that has clinical data on HDL delivery, with a delivery vehicle (CER-001) which has demonstrated safety and tolerability in humans. TARGET is our first step for our platform in the clinic and this imaging study in patients supports targeting cells which over-express HDL receptors, such as tumor cells, in order to deliver active pharmaceutical drugs. It further reinforces our intent to leverage our know-how and our proprietary intellectual property to move forward into immuno-oncology and chemotherapy."

Professor Dr. Erik Stroes, comments: "The concept of targeted delivery to cancer using nanoparticles is highly attractive. However, historical nanoparticle platforms have failed to deliver on their promise (on average, only 0.7% of the administered nanoparticle dose has been found to be delivered to solid tumors[5] which can lead to undesirable systemic and toxic side effects). HDL is a naturally occurring particle in humans, which can be loaded with exogenous compounds, leading to a unique and safe local delivery strategy in humans. Our data in TARGET suggest the potential for greatly enhanced delivery to specific cellular targets. HDL interacts with a number of HDL receptors including the scavenger receptor B-I (SR-BI), which is highly expressed in certain cancers. Thus these preliminary results are very encouraging and open many opportunities."

Professor Dr. Hanneke Van Laarhoven, MD, PhD, concludes: "TARGET preliminary data support CER-001 targeting particles promise to markedly increase the amount of drug delivered to cancer cells in

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tomography (CT) scanner, to acquire sequential images from both devices in the same session, which are combined into a single superposed (co-registered) image. Thus, functional imaging obtained by PET, which depicts the spatial distribution of metabolic or biochemical activity in the body can be more precisely aligned or correlated with anatomic imaging obtained by CT scanning. Two- and three-dimensional image reconstruction may be rendered as a function of a common software and control system.

[2] *J Nucl Med August 1, 2015 vol. 56 no. 8 1272-1277*

[3] *Front. Pharmacol.* **7**, 466 (2016).

[4] *TNM classification: International classification that reports on the stage of cancer progression. The letter T is the tumor initial and corresponds to the size of the tumor; the letter N (for Node) indicates whether or not lymph nodes have been invaded; the letter M (for Metastasis) indicates the presence or absence of metastases*.

[5] *Nature Reviews Materials* **volume 1**, Article number: 16014 (2016)

our patients. The fact that a wide variety of drugs can be embedded in HDL nanoparticles could increase efficacy compared to available drug delivery technologies and open a new generation of drugs in oncology. Targeted delivery also holds the promise of safer chemotherapeutic regimens. Despite medical progress in the diagnosis and treatment of esophageal cancer, 5-year overall survival rates remain poor, underlining the critical need for novel treatment strategies. We believe that the TARGET study results will offer new hope."

About CERENIS: www.cerenis.com

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

In addition to advancing HDL technologies for drug delivery, CERENIS is developing a portfolio of lipid metabolism therapies, including HDL mimetics for patients with genetic HDL deficiency, as well as drugs which increase HDL for patients with a low number of HDL particles to treat atherosclerosis and associated metabolic diseases including Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steato-Hepatitis (NASH). CERENIS is well positioned to become one of the leaders in the HDL therapeutic market, with a broad portfolio of programs in development.

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. SAMBA, the clinical Phase II study in patients with hypoalphalipoproteinemia due to genetic defects, has provided important data demonstrating the efficacy of CER-001 in regressing atherosclerosis in several distinct vascular beds, and leading to the TANGO study with results expected at the end of 2018. 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 on the market.

About Target

The TARGET study is an investigator initiated single-center observational trial enrolling 10 adult subjects with a pathologically proven diagnosis of primary esophageal carcinoma in situ. Patients are at least all T2 staged according to the TNM classification.

The aim of the TARGET study is to assess the concentrations of Zirconium 89 labeled CER-001 in tumor tissue at three time points after a single administration (1, 24 and 72 hours). Recent pre-clinical studies have demonstrated that reconstituted radio-labeled HDL nanoparticles may be used to label tumors, with specificity for tumor associated macrophages. Furthermore, in cancer patients, ^{89}Zr-labeled HDL mimetic CER-001 will allow for non-invasive evaluation of the potential of drug delivery strategies in selected cancers. Success will pave the way for loading of HDL nanoparticles with immune-oncology and chemotherapeutic agents.

The investigational product is CER-001, a pre-beta HDL mimetic labeled with Zirconium-89 for serial PET/CT imaging in patients. It has been demonstrated that CER-001 pre-beta HDL mimetic could be used as a tumor imaging product to validate that HDL specifically target tumors via HDL receptors in patients. CER-001 has a very favorable safety and tolerance profile as demonstrated in previous clinical trials.

About Targeted HDL Drug Delivery

HDL particles, loaded with an active agent, hold the promise to target and selectively kill malignant cells while sparing healthy ones. A wide variety of drugs can be embedded in these particles targeting markers specific to cancer cells and bring these potent drugs to their intended site of action, with lowered systemic toxicity.
Cargomer™, apo-AI multimeric nanoparticles, and HDL particles such as CER-001 have the future potential to serve as carriers of multiple anti-cancer drugs, antigens, interfering RNA (siRNA's), and anti-sense oligonucleotides (ASOs) opening the path for the Cerenis platform.
Cerenis intends to develop the first HDL-based targeting drug delivery platform dedicated to the oncology market, including immuno-oncology and chemotherapy.

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Contacts:

Cerenis
Jean-Louis Dasseux
CEO
info@cerenis.com
+33 (0)5 62 24 09 49

NewCap
Investors relations
Emmanuel Huynh / Louis-Victor Delouvrier
cerenis@newcap.eu
+33 (0)1 44 71 98 53

NewCap
Media relations
Nicolas Merigeau
cerenis@newcap.eu
+33 (0)1 44 71 94 98