



Cytheris Announces Initiation of ORVACS-Sponsored Phase II Clinical Study combining Immunomodulatory Intervention with Interleukin-7 (CYT107) and Antiretroviral Intensification with Raltegravir and Maraviroc to Attack the Viral Reservoir of HIV Patients

By combining an integrase inhibitor and a CCR5 inhibitor with IL-7 to target or induce activation of latently infected cells, study aims to investigate whether exhausting the HIV reservoir and ultimately obtaining virus eradication is feasible

Paris – October 19, 2010 – Cytheris SA, a clinical stage biopharmaceutical company focused on research and development of new therapies for immune modulation, today announced the initiation of Phase II clinical trial of the company's investigative immunomodulatory agent, CYT107 (rhIL-7), in combination with two potent antiretroviral drugs represented by the integrase inhibitor raltegravir (ISENTRESS® - Merck & Co.) and the CCR5 inhibitor, maraviroc (SELZENTRY™ - ViiV Healthcare). The main hypothesis of this study is that by combining the most potent and synergistic antiretroviral drugs, coupled with an immunomodulating agent capable of targeting or inducing activation of latently infected cells, the reservoirs of HIV can be decreased and, in the best case scenario, eradication of the virus may be feasible.

The trial, known as EraMune 01, is designed and sponsored by the French not-for-profit institution Objectif Recherche VACCin Sida (ORVACS) with financial support from the Bettencourt-Schueller Foundation, Paris, France. Since its creation in 2001, ORVACS, together with the support of its international network of excellence, has focused its resources and efforts, on the development of innovative immunotherapeutic and vaccine strategies against HIV. Under the direction of Prof. Christine Katlama, MD (Principal Investigator), Head of the AIDS Clinical Research Unit, Department of Infectious Diseases, Hopital Pitie-Salpetriere, Paris, France, and Bonaventura Clotet, MD, PhD (co-Principal Investigator), Chief of the Internal Medicine HIV Unit, University Hospital Germans Trias i Pujol, Barcelona, Spain, the study will be conducted at clinical sites in France, Spain, Italy, and the United Kingdom.

The EraMune 01 study, "International, multicenter, randomized, non-comparative controlled study of therapeutic intensification plus immunomodulation in HIV-infected patients with long-term viral suppression," is a further investigation of Cytheris' promising investigative immunotherapy, CYT107 (recombinant human interleukin-7, or IL-7), already the subject of seven other studies for different indications.

"The novelty of the approach in this study is three-fold," said Prof. Katlama. "First, the use of highly potent antiretroviral therapy combining drugs with different HIV enzyme targets or receptors and different penetrations in cells, to suppress the virus to truly undetectable levels; secondly, the addition of an immunomodulatory therapy that specifically targets viral reservoirs; and lastly, the rigorous selection of patients already having a low HIV reservoir as measured by peripheral blood HIV DNA content."

Eradication of HIV from an infected individual cannot be achieved by any of the current antiretroviral drug regimens in use today. To date, the failure to eradicate HIV has been due to viral persistence in reservoirs that are established early in the infection and are insufficiently affected by antiretroviral therapy, and thus are able to replenish systemic infection whenever treatment is interrupted. Highly active antiretroviral therapy can reduce plasma viral load below detectable limits in most patients. However, the current therapies target various steps in the virus life cycle, which results only in prevention of new infection with little impact on already infected cells or the integrated provirus.

"IL-7 in combination with conventional antiretroviral therapy has demonstrated in early clinical studies that it promotes restoration of T cell numbers and function and induces some HIV replication in the CD4⁺ T cell subset, including quiescent T cells, while also expanding the pool of uninfected CD4⁺ T cells," said Thérèse Croughs, MD, Chief Medical Officer of Cytheris. "The unique hypothesis tested in this study is that with a novel antiretroviral therapy combination complemented by entry and integrase inhibitors, the induction of viral replication from quiescent CD4⁺ T cells can be contained by the complementary HIV inhibitors while remaining sufficient to expose infected cells to immune elimination, eventually contributing to viral reservoir reduction and potential eradication."

In the last two decades, 27 antiretroviral drugs have been approved by the FDA and EMEA, including two new recently approved classes of drugs, the integrase inhibitor raltegravir (ISENTRESS® - Merck & Co.) and the CCR5 inhibitor, maraviroc (SELZENTRY™ - ViiV Healthcare). The goal of eradication of HIV from the host has resurfaced because of these additional new classes of drugs.

One of the most exciting areas in HIV treatment and research today involves the integrase inhibitors. Integrase is an HIV viral enzyme that is essential for viral replication. Inhibitors of integrase are completely independent in their activity compared to all other antiretroviral drug classes including reverse transcriptase, protease, maturation and entry inhibitors. Viruses resistant to all known drugs therefore, remain completely susceptible to integrase inhibitors. Additionally, integrase inhibitors are active in both CCR5-tropic and CXCR4-tropic HIV-1 viruses.

The overall strategy of the ERAMUNE 01 trial is to treat selected patients with an optimal synergistic antiretroviral regimen plus one or more immunomodulating agents.

In summary, the ERAMUNE Program proposes a proof of concept strategy that combines the association of novel safe and very potent ARVs with an optimized cART regimen plus an immune experimental intervention that would activate the latently infected cells in order to purge the reservoir of HIV-infected patients while the antiviral combination would block the spread of the virus. The patients will be selected on the basis of a low peripheral blood reservoir. The proposed immune intervention has been shown to be safe in vivo. The concept will ultimately test whether exhausting the HIV reservoir and ultimately obtaining virus eradication is feasible. If successful, this would open the door for more innovative approaches that would be capable of eradicating the virus in a broader spectrum of patients.

About the Study – www.clinicaltrials.gov

Antiretroviral therapy (ART) has been one of the most successful fields of therapeutic research in the last twenty years. The extensive use of highly active antiretroviral therapy (HAART) since 1996 has led to a marked decrease in morbidity and mortality of HIV-1 infection, transforming a uniformly lethal disease into a chronic infection¹. The goal of therapy is a durable suppression of viral replication, the almost unique condition for immune reconstitution, control of disease progression, prevention of the emergence of drug resistance, and, ultimately, potentially normal life span. However, in the absence of any alternative treatment to durably control viral replication and the lack of current strategy to eradicate HIV from an infected person, antiretroviral therapy has to be administered life-long. Nevertheless, life-long use of antiretroviral therapy raises other crucial issues such as long-term tolerability and compliance, risk of emergence of resistance in case of incomplete viral suppression, sustainability of drugs supplies worldwide.

The first step in developing a new therapy and the focus of this study is to explore the strategy of ARV treatment intensification with the addition of an immunomodulating agent that can activate latently-infected cells. This will be undertaken in a pilot study in patients with fully controlled HIV replication as measured by viral RNA and cell-associated HIV DNA. The first proof of concept clinical study outlined here will include 28 patients, each randomized in an open label non-blinded manner to one of two study arms (14 per group):

- A. Antiretroviral intensification (cART + raltegravir and maraviroc)
- B. Antiretroviral intensification + immunomodulatory intervention (added after 8 weeks of antiretroviral intensification) with 2 cycles of 3 r-hIL-7 (CYT107) injections.

Primary objective:

- Important decrease in the HIV-1 viral reservoir

Secondary objectives:

- Eradicate HIV in the lymphoid reservoirs of HIV in the gut
- To describe the immunologic effects of treatment intensification with and without immunomodulatory therapy
- Develop a model for HIV DNA decay in patients receiving treatment intensification with and without immunomodulatory therapy
- Determine the safety of treatment intensification with and without immunomodulatory therapy.

About Interleukin-7 (CYT107)

Recombinant human interleukin-7 (CYT107) is a critical immune-modulator for immune T-cell recovery and enhancement. As a growth factor and cytokine physiologically produced by marrow or thymic stromal cells and other epithelia, IL-7 has a critical and, at some steps, a non-redundant stimulating effect on T lymphocyte development, notably on thymopoiesis and, downstream from the thymus, on homeostatic expansion of peripheral T-cells.

A first-generation form of rhIL-7 was shown in pre-clinical and Phase I studies in oncology and HIV-infected patients to be well tolerated in repeated dose trials, with long-lasting increases in both CD4 and CD8 T cells. CYT107 is a second-generation rhIL-7 product made by Cytheris via a recombinant mammalian cell culture system.

Clinical trials conducted on more than 160 patients (90 with CYT107) in Europe, North America and Taiwan have demonstrated the potential of IL-7 to expand and protect CD4+ and CD8+ T-cells. Currently, Cytheris is conducting multiple international investigations of IL-7 in HIV, HCV, HBV, post-BMT and cancer. Additional studies include a NIAID/NIH-sponsored trial in idiopathic CD4 lymphocytopenia (ICL) and a cancer vaccine study in children with Ewing's sarcoma family of tumors or similar genetic tumors sponsored by US National Cancer Institute.

About Cytheris – www.cytheris.com

Cytheris SA is a privately held clinical-stage biopharmaceutical company focused on research and development of new therapies for immune modulation. These drugs aim at reconstituting and enhancing the immune system of patients suffering from cancer, chronic viral or bacterial infections such as HCV, HBV and HIV, or lympho-depleting treatments such as chemotherapy, radiotherapy, bone marrow transplantation (BMT) and hematopoietic cell transplantation (HCT). The company operates from its headquarters and laboratories in Issy-les-Moulineaux, a suburb of Paris, and its U.S. subsidiary in Rockville, Maryland.

For more information, please contact:

International media inquiries -- Andrew Lloyd & Associates:

Andrew Lloyd (allo@ala.com), Neil Hunter (neil@ala.com)

Tel: +44 1273 675 100

#