



Cytheris Announces Initiation of NIAID/NIH-Sponsored Phase I/IIa Clinical Trial of Interleukin-7 (IL-7)

Study to focus on immunotherapy for treatment of idiopathic CD4 lymphocytopenia (ICL), a rare condition for which no treatment currently exists

Paris – October 14, 2009 – Cytheris SA, a clinical stage biopharmaceutical company focused on research and development of new therapies for immune modulation, today announced the initiation of a Phase I/IIa dose escalation study of patients suffering from idiopathic CD4 lymphocytopenia (ICL). ICL is a rare, orphan disease characterized by abnormally low CD4 T cell counts without evidence of human immunodeficiency virus (HIV-1 or HIV-2) infection. The trial is a further investigation of Cytheris' promising investigative immunotherapy, CYT107 (recombinant human interleukin-7, or IL-7), already the subject of six other studies for different indications.

The study is sponsored, conducted and partially funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health (NIH). Under the direction of Irini Sereti, M.D., M.H.S., NIAID/NIH Study Investigator, the trial is designed to assess the safety and biological effects of repeated administration of CYT107 and will be conducted at the NIH Clinical Center in Bethesda, Maryland, the largest US hospital devoted entirely to clinical research.

"Since its inception in 1999, Cytheris has had a close relationship with IL-7 investigators at the US National Institutes of Health, a connection that has played a pivotal role in bringing the potential of this cytokine to the attention of the medical community," said Michel Morre, DVM, President and CEO of Cytheris. "We are very pleased that NIH has again recognized the value of the IL-7 program and has chosen to provide financial support as well as the participation of NIAID investigators in this clinical development program focused on ICL."

The trial is called ICICLE (**I**nterleukin-7 (**C**YT107) Treatment of **I**diopathic **C**D4 **L**ymphocytopenia: **E**xpansion of CD4 T Cells). It is a Phase I/IIa open-label, single arm clinical trial evaluating the safety profile of glycosylated recombinant human interleukin-7 (rhIL-7) as an immune modulator in patients with ICL at risk of disease progression. Secondary analyses will assess the immunostimulatory effects of rhIL-7 on T cell numbers and function.

"ICL patients have a propensity to develop serious co-morbidities and the dearth of treatment options for their primary lymphocytopenia, particularly in patients who have experienced opportunistic or otherwise serious infections, means that the unmet medical need to establish novel immune treatments for ICL patients persists," said Thérèse Crouchs, MD, Chief Medical Officer of Cytheris. "IL-7 represents a promising investigative therapy which has shown in pre-clinical and Phase I studies in oncology and in HIV-infected patients to be well tolerated in repeated dose trials, with long-lasting increases in both CD4 and CD8 T cells."

Study Design and Objectives

This is a single center, open-label, single-arm, Phase I/IIa interventional clinical trial. The study population is defined as men and women, aged ≥ 18 years, with a confirmed diagnosis of ICL (CD4 < 300 cells/ μ L or $< 20\%$ of lymphocytes on two occasions) deemed at risk for complications due to concurrent CD8 T cell lymphocytopenia and/or a history of opportunistic or otherwise serious infection, without autoimmunity or hematologic or lymphoid malignancy.

Participants will be evaluated at baseline (prior to study treatment) and according to the protocol follow-up schedule, receive a total of 2 cycles of subcutaneous rhIL-7 (CYT107) dosed once weekly for 3 weeks in a dose escalation fashion: 3 μ g/kg (first 5 volunteers), 10 μ g/kg (next 5 volunteers) and 20 μ g/kg (last 5 volunteers), with an additional 5 study participants at the highest achieved dose level. Cycles of rhIL-7 will be administered starting at Week 1 and Week 24.

Approximately 35-40 patients will be screened over a 3-year period to achieve the desired sample of 20 ICL patients. Safety assessments of rhIL-7 will be the primary focus at each study visit, with secondary analyses of immune parameters, including changes from baseline in T cell numbers and function, at Weeks 24 and 48. Enrollment is expected to take 3 to 4 years. Each volunteer will be followed for 48 weeks. Thus, total duration of the study will be approximately 5 years.

The exploratory objectives of this study are to evaluate the immunomodulatory effects of rhIL-7:

- Evaluate changes in CD4 and CD8 T cell counts
- Evaluate whether any observed changes in CD4 and CD8 T cell counts are due to increasing thymic output and/or peripheral T cell expansion
- Evaluate effects on T cell activation status
- Evaluate effects on the function and proliferation of antigen-specific T cells
- Evaluate effects on gastrointestinal mucosal lymphocytes
- Evaluate effects on lymph node-based tissue lymphocytes
- Evaluate predictors of response (i.e., increases in CD4 T cells), such as age, baseline total and naïve CD4 T cell counts, baseline CD127 expression on T cells, and MHC haplotype

The restorative effects of exogenous IL-7 on the immune system of ICL patients will be assessed by both flow cytometric immunophenotyping and lymphocyte functional assays to assess the following:

- CD4 and CD8 T cell counts
- Naïve and memory T cell subsets
- Naïve T cells representing recent thymic emigrants
- Activated and proliferating T cells
- T cell apoptosis and survival
- T cell receptor (TCR) repertoire

Additional information on the ICICLE study can be found at clinicaltrials.gov.

About Interleukin-7 (CYT107)

Recombinant human interleukin-7 (CYT107) is a critical growth factor 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 110 patients 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 HCV, HIV and cancer, with trials for other indications planned to initiate in 2H09.

About Cytheris' Interleukin-7 Clinical Development

Ongoing clinical development includes six interpatient dose escalation studies, with starting doses varying from 3 µg/kg/week to 60 µg/kg/week, to evaluate the safety and biological activity of CYT107 in various indications. These studies include:

- **CLI-107-04:** a monocentric Phase I interpatient non-controlled dose escalation study in oncology (metastatic melanoma or renal cell carcinoma), conducted at the US National Cancer Institute, Bethesda, Maryland.
- **CLI-107-06 (the INSPIRE study):** a Phase I/IIa interpatient dose escalation randomized placebo-controlled, single-blind, multicenter study in HIV-infected patients, conducted in the United States, Canada, Italy and France.
- **CLI-107-05 (ECLIPSE-1):** a Phase I multicenter, non-controlled interpatient dose escalation study in treatment-naïve, non-responder (no Early Viral Response (EVR) at week 12) HCV infected patients conducted in France, Italy and Switzerland assessing CYT107 in combination with a peg-interferon (peg-IFN) and Ribavirin (RBV) bi-therapy.

- **CLI-107-07 (ECLIPSE-2):** a Phase I/IIa non-controlled dose escalation study in HCV-infected patients, conducted in France and Italy, evaluating CYT107 in combination with peg-IFN and RBV bi-therapy in patients with genotype 1 and 4 previously non-responsive to standard treatment.
- **CLI-107-09 (ECLIPSE 3):** a Phase I/IIa non-controlled dose escalation study in chronically infected HCV patients, conducted at multiple sites in Taiwan, evaluating CYT107 in combination with peg-IFN and RBV bi-therapy in patients with genotype 1 previously non-responsive to standard treatment.
- **CLI-107-08:** a monocentric Phase I non-controlled interpatient dose escalation study in recipients of HLA-matched ex-vivo T-cell-depleted bone marrow or peripheral blood stem cell transplant to restore CD4+ and CD8+ counts following T-cell depletion, conducted at the Memorial Sloan-Kettering Cancer Center in New York City.

About ICL

Idiopathic CD4 lymphocytopenia (ICL) was first systematically described in 1993 in a group of adolescent and adult patients with abnormally low CD4 T cell counts without evidence of human immunodeficiency virus (HIV-1 or HIV-2) infection. This case series followed the formal definition of ICL a year earlier by the US Centers for Disease Control and Prevention (CDC) as having a persistently low CD4 T cell count of <300 cells/ μ L or <20% of total T lymphocytes, measured on at least 2 occasions 6 weeks apart. Excluded from this diagnosis are individuals with known HIV or human T-cell lymphotropic virus (HTLV) infection, concurrent malignancy, immunosuppressive therapy (e.g., corticosteroids, anti-metabolites), or any other co-morbidity known to cause secondary lymphocytopenia.

Thus, an ICL diagnosis is typically established over time, following the treatment of concurrent infections or other underlying disorders, as lymphocyte subsets are assessed during periods of relative homeostasis, apart from acute illness. Several cohort studies have identified this rare condition in 0.25% to 0.5% of healthy blood donors, with the frequency of symptomatic ICL patients being significantly lower.

ICL patients are a heterogeneous group that may display concurrent CD8 T cell, B cell, or natural killer (NK) T cell lymphocytopenia, and whose clinical manifestations range from asymptomatic to life-threatening infections, including opportunistic pathogens, such as *Cryptococcus* and non-tuberculous *Mycobacteria*, with a significant incidence of de novo malignancies and autoimmune phenomena (e.g., systemic lupus erythematosus, anti-phospholipid antibody syndrome).

A unifying etiology for this disorder has yet to be identified, and few studies have characterized representative cases immunologically, particularly regarding lymphocyte responses to immunostimulatory cytokines.

There are no clear guidelines regarding prophylaxis against opportunistic infections or primary therapy for the underlying T cell immunodeficiency in ICL patients. Treatment of concurrent infections, malignancies, and autoimmune disorders is currently the standard of care.

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.

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