



Cytheris Initiates Asian Phase I/IIa Clinical Trial of Interleukin-7 (IL-7) as an Immunotherapy in HCV Patients

Taiwan trial studies patients who failed to achieve SVR with standard treatment, and complements Company's two other investigations in naïve and previously non-responsive HCV patients currently ongoing in Europe

Paris – October 28, 2008 – Cytheris SA, a clinical stage biopharmaceutical company focused on research and development of new therapies for immune modulation, today announced the initiation of a multicenter Phase I/IIa dose escalation study in Taiwan. This study will assess the safety and tolerability of repeated administration of Cytheris' investigative immunotherapy, recombinant human Interleukin-7 (CYT107), as an add-on therapy in the treatment of patients infected with genotype 1 hepatitis C (HCV) and who previously have proven non-responsive to standard treatment. The study will be conducted at four sites, two in Taipei and one each in Tainan and Kaohsiung.

The trial (CLI-107-09) is called ECLIPSE-3 (**E**valuation in hepatitis **C** Liver disease of **IL**-7 in a **P**hase I/IIa **S**tudy of dose **E**scalation in Taiwan) and follows two other ongoing ECLIPSE studies (see below). It will evaluate (at Week 12) the safety of biologically active doses of CYT107 added to a combination therapy of pegylated interferon-alpha (peg-IFN) and ribavirin (RBV) in Asian patients with chronic infection by genotype 1 HCV who have not responded to this combination therapy (no EVR after Week 12 or no response after 24 or 48 weeks).

"In addressing these patients who have failed to respond to the standard interferon-based treatment for HCV, we are confronting a significant unmet medical need faced by people and healthcare systems on a global scale," said Michel Morre, DVM, President and CEO of Cytheris. "After failing the standard combination therapy, patients and their physicians are left with virtually no available treatment options that can arrest this silent but nevertheless progressive liver disease."

Study Design and Objectives

This is a multicenter, Phase I/IIa inter-patient dose escalation study. Patients chronically infected with HCV genotype 1 will be assessed for study participation if, based on past treatment history, they are considered resistant to standard bitherapy treatment with peg-IFN and RBV (no EVR at Week 12 or HCV RNA detectable at Week 24 or Week 48). Standard bitherapy will be initiated in these previously treated "non-responder" HCV infected patients and administered for 6-10 weeks. CYT107 will then be added for a cycle of four weekly subcutaneous injections at defined dose levels while standard bitherapy is continued for 9 weeks after CYT107 treatment is discontinued. The duration of the study is approximately 60 weeks, with at least 20-25 weeks of bitherapy.

In addition to assessing the safety of biologically active doses of CYT107 added to the standard bitherapy treatment, secondary objectives of the investigation include:

- characterization of the pharmacokinetics and pharmacodynamics of CYT107 in the study population;
- evaluation of the potential anti-viral effect of CYT107 in the context of a dose escalation strategy following completion of CYT107 treatment at Week 4 and Week 12;
- documentation of the long-term safety and viral load variations at Week 24 and Week 48 following the first CYT107 injection;
- study of the evolution of CD3, CD4, CD8 and CD19 cell counts from baseline (before CYT107 administration) to Week 12 and during long-term follow-up at Week 24 and Week 48;
- evaluation of the immune specific response to HCV;
- recommendation of a dose and administration schedule for CYT107 that will define a basic cycle of treatment for Phase IIb/IIIa development studies in patients with chronic HCV infection resistant to peg-IFN and RBV therapy.

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, down-stream from the thymus, on homeostatic expansion of peripheral T-cells.

Clinical trials conducted on more than 80 patients in Europe, the US and Canada 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 in other indications planned to initiate in 1H09.

About Interleukin-7 Clinical Development

Ongoing clinical development includes five interpatient dose escalation studies, with starting doses varying from 3 µg/kg/week to 30 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 dose escalation non-controlled study in oncology (metastatic melanoma or renal cell carcinoma), conducted at the National Cancer Institute, Bethesda, Maryland, (United States).
- **CLI-107-06 (the INSPIRE study):** a Phase I/IIa interpatient dose escalation randomized placebo controlled single-blind multicenter study in chronically HIV infected patients conducted in the United States, Canada, Italy and France.
- **CLI-107-05 (ECLIPSE-1):** a Phase I interpatient dose escalation non-controlled multicenter study in treatment naive, non-responder (no EVR at week 12) HCV infected patients conducted in France, Italy and Switzerland assessing CYT107 in combination with a peg-IFN and RBV bitherapy.

- **CLI-107-07 (ECLIPSE-2):** a Phase I/IIa dose escalation non-controlled 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-107-08:** a monocentric Phase I interpatient dose escalation non-controlled 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 HCV

Hepatitis C is a blood-borne virus recognized as a major cause of chronic hepatitis and a global health problem. WHO estimates that about 180 million people, some 3% of the world's population, are infected with HCV, 130 million of whom are chronic carriers at risk of developing liver cirrhosis and/or liver cancer. It is estimated that three to four million persons are newly infected each year, 70% of whom will develop chronic hepatitis. HCV is responsible for 50–76% of all liver cancer cases and two-thirds of all liver transplants in the developed world. Of the new cases occurring each year, about 25% are symptomatic, but 60 to 80% may progress to chronic liver disease, and 20% of these develop cirrhosis. About 5 to 7% of patients may ultimately die of the consequences of the infection. In the US alone, the CDC projects that between 2010 and 2019, direct medical costs due to HCV-related liver disease will reach \$10.7 billion, representing a substantial health and economic burden over the next 10 to 20 years.

The overall prevalence of HCV infection is 1 to 2% in most countries where studies have been conducted, but the distribution of HCV varies considerably among populations. For instance, the prevalence of HCV is low (< 1%) in Australia, Canada and northern Europe, between 1 and 2% in the US (4 million infected carriers) and most of Europe (5 million infected carriers), and high (>2%) in many countries in Africa, Latin America and Asia, where prevalence figures between 5 and 10% are frequently reported. For instance, WHO estimates that there are 25 million HCV-infected carriers in the 9 countries of the South-East Asian region, 12 million of whom live in India.

In Taiwan, prevalence of the disease in the general population ranges from 2% to as high as 6% in some counties, with approximately 0.9 million people infected on the island. In mainland China, HCV has become one of the country's major health issues, with a prevalence rate of 2.2% in the general population (but much higher in certain rural provinces) amounting to more than 25 million infected individuals.

About HCV Treatment

Currently, there is no specific antiviral agent directed against HCV that is commercially available, and no vaccine for prevention of infection. A number of small molecules inhibiting HCV polymerase or protease are in development and seem likely, if approved, to be candidates for combination therapy with an immuno-modulating agent such as CYT107. In such combination, CYT107 may complement the antiviral molecule's achievement of lowered viral load by improving immune system control and thereby facilitating eradication of HCV infection. Several interferon products are available worldwide, but there are substantial limitations to the use of these products

when given as monotherapy or in conjunction with ribavirin in the treatment of chronic HCV infection. In "naïve" patients, those never treated with interferon or ribavirin, SVR is achieved with the 48-week combined therapy in less than 50% of patients infected by HCV genotype 1 or 4 in Western countries, and between 60% and 80% in Asian countries, including Taiwan. In addition to the relatively poor treatment response in patients infected with genotype 1 HCV, the most common strain in the U.S., Western Europe, Japan, and Taiwan, the considerable side effects frequently associated with the use of interferon leads to discontinuation of therapy in approximately 10-20% of treated patients.

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 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:

French/International media inquiries -- Andrew Lloyd & Associates:

Andrew Lloyd (allo@ala.com), Cécilia Derrien (cecilia@ala.com)

Tel: +33 1 5654 0700

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