



## **Cytheris Announces Initiation of CONVERT, a Phase I/IIa Study of Recombinant Human Interleukin-7 (CYT107) in Combination with Antiviral Therapy and Vaccination for Treatment of Chronic Hepatitis B Virus**

### **Initiation of CYT107 Study in HBV Expands Company's Hepatitis Investigations, Which Include Three Ongoing Studies in Hepatitis C (HCV)**

*Paris (France) – December 8, 2009* – Cytheris SA, a clinical stage biopharmaceutical company focused on research and development of new therapies for immune modulation, today announced that it has begun enrolling patients in its Phase I/IIa clinical program evaluating the company's investigative immune-modulator, recombinant human Interleukin-7 (CYT107), in combination with standard antiviral treatment and vaccination in HBeAg-negative chronic hepatitis B-infected (HBV) patients.

"Cytheris is currently conducting three clinical trials of CYT107 in chronic hepatitis C-infected patients in Europe and Asia," said Michel Morre, DVM, President and CEO of Cytheris, "and we are now pleased to initiate CONVERT in chronic hepatitis B infection here in Europe, underscoring our dedication to exploring new treatment options for the millions of patients throughout the world afflicted with these devastating viral infections."

"Though the most effective HBV antiviral drugs have shown a remarkable ability to rapidly drop HBV viral load, even with these powerful drugs the percentage of patients reaching HBsAg seroconversion -- the ultimate goal of therapy -- remains low," said Christophe Hézode, MD, of the Department of Hepatology-Gastroenterology at Hospital Henri Mondor, Creteil, France, Principal Investigator and International Study Chairman for the trial. "This failure to cure the disease explains why investigators have tried to boost long-term immunological response through patient vaccination or immunomodulation, though these attempts have so far been insufficient to fully control the disease. It is our hope that combining IL-7 with an antiviral and a vaccine will ultimately result in the production of a protective and long lasting immune response against the HBV virus in a significant proportion of treated patients."

### **About the Study (CLI-107-10)**

CONVERT is a randomized open label, controlled multicentre Phase I inter-patient dose escalation study, followed by a Phase IIa extension of 1 or 2 dose levels of CYT107 which have demonstrated safety and sufficient immunological or antiviral activity.

The primary objective of the study is to determine the short and long-term safety and biological activity of CYT107 in patients with a HBeAg-negative chronic hepatitis B virus who have, at screening, undetectable HBV DNA and who have been stable for at least 3 months with antiviral treatment.

The trial will initiate at 7 study centers in France and 3 sites in Italy.

At each dose level, two cohorts of 4 patients, 3 treated with CYT107 and 1 control patient, will be run in parallel. The treatment of the two cohorts is characterized by the following:

- Tri-therapy group: patients will receive CYT107 + HBV vaccine (GenHevac B Pasteur®) + antiviral treatment [BARACLUDE® (entecavir) or VIREAD® (tenofovir)] and one control patient will receive only antiviral treatment.
- Bi-therapy group: patients will receive CYT107 + antiviral treatment (entecavir or tenofovir) and one control patient will receive antiviral treatment only.

Patients with chronic HBeAg-negative hepatitis will be assessed for study participation if they have undetectable HBV DNA for at least 3 months when treated with entecavir or tenofovir. For all included patients the antiviral therapy will be continued during the full duration of the study. Patients will be followed up to Week 48, with a mid-term evaluation of the biological activity at Week 16.

According to Thérèse Crouchs, MD, Chief Medical Officer of Cytheris, "The combination of three factors is expected to result in producing a protective immune response against the HBV virus in a significant proportion of patients:

1. The severe drop in viral load produced by HBV antivirals such as entecavir or tenofovir will decrease the frequency of PD-1 expressing T cells and rescue them from exhaustion, leaving room for protective T cells expressing the IL-7 receptor (CD127<sup>+</sup>);
2. The repeated administration of GenHevac B Pasteur® vaccine should support the production of anti-HBV specific T cells, including central memory T cells, and it is these cells that will be further augmented and supported by CYT107 treatment; and,
3. The cycle of CYT107 treatment will both facilitate the production of naïve CD4 and CD8 T cells available for specific antigen response and support the production of long lived central memory specific T cells."

The restoration of a specific immune response should translate into HBsAg seroconversion together with direct elimination of residual viral DNA. Moreover, the anti-fibrotic effects of CYT107 may prevent or slow the evolution to cirrhosis. In this early clinical study, the aim will be to better understand how to optimize this combined therapeutic approach to favor a shortened treatment regimen through induction of a protective and long lasting immune response.

### **About Hepatitis B**

Hepatitis B virus (HBV) is a hepatotropic non-cytopathic DNA virus, which is transmitted percutaneously, sexually and perinatally. Two billion people in the world are estimated to be infected with the hepatitis B virus. Chronic infection with HBV is a major cause of liver disease, ranking as a substantial cause of cirrhosis and hepatocellular carcinoma (HCC). An estimated 350 to 400 million people are living with chronic HBV infection which annually accounts for 1 million deaths from cirrhosis, liver failure, and hepatocellular carcinoma, representing 30% of all cirrhosis cases and approximately 50% of all HCC cases worldwide.

The incidence of acute HBV infection has decreased dramatically in Western countries since the mid-1980s following the introduction of an effective vaccine: in the U.S., the incidence in the general population decreased by 75% between 1990 and 2004, a reduction which can be attributed to the availability of an effective vaccine and widespread immunization of infants and high-risk populations.

The same is true for Europe, where in Germany the incidence of reported acute HBV cases dropped from 7.5 cases/100,000 inhabitants in 1995 to 1.4 in 2005, and in Italy, where a similar trend was observed following introduction of the anti-HBV vaccination for newborns and young children in 1991.

In low endemic countries HBV is usually acquired via injection drug use, sexual contacts, or body piercing activities, while in endemic regions (seroprevalence  $\geq 8\%$ ), such as Asia, most infections are acquired perinatally.

Currently available options for the treatment of chronic HBV infection include standard and pegylated interferon  $\alpha$  and five oral antiviral agents (lamivudine, adefovir, entecavir, tenofovir and telbivudine). According to a recent comprehensive literature search, entecavir efficacy is superior to that of lamivudine, which in turn would be superior to that of adefovir in nucleoside-naïve patients with chronic HBV infection. Low doses of tenofovir are also more potent than adefovir in chronic HBeAg negative hepatitis B.

Available antiviral treatments, especially entecavir and tenofovir, have been shown to induce a remarkable and rapid drop of HBV viral load as measured by viral DNA. However, even with these powerful drugs the percentage of patients reaching HBsAg seroconversion remains extremely low and the viral load increases at the end of treatment.

### **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 120 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 HIV, HCV, idiopathic CD4 lymphocytopenia (sponsored by NIAID/NIH) and cancer, the latter including an NCI/NIH-sponsored study of IL-7 in combination with dendritic cell vaccines in a pilot study of tumor vaccination in children and a study designed to restore CD4+ and CD8+ counts following T-cell depletion due to bone marrow or peripheral blood stem cell transplant (being conducted at the Memorial Sloan-Kettering Cancer Center in New York City).

### **About Cytheris – [www.cytheris.com](http://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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