Gilead Begins Multinational Phase III Trial of Hepatitis B Drug, Adefovir Dipivoxil

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Phase II Data Show Rapid Reduction of Virus Levels by 99.99% and 20% Seroconversion

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Gilead Sciences, Inc. (Nasdaq: GILD) announced today that it has begun randomization of patients in a multinational Phase III clinical trial of adefovir dipivoxil for the treatment of chronic hepatitis B virus (HBV) infection. The study is designed to enroll a total of 500 patients at nearly 100 sites in the United States, Canada, Europe, Australia and Southeast Asia. This trial is the first in a series of pivotal studies Gilead intends to sponsor to further define the role of adefovir dipivoxil in the management of this widespread disease.

Formulated as a pill taken once daily, adefovir dipivoxil has demonstrated antiviral activity against a broad spectrum of viruses, including HBV, human immunodeficiency virus (HIV) and herpesviruses. Adefovir dipivoxil is a nucleotide analogue from a class of antivirals shown to be long acting, potent inhibitors of viral replication with unique resistance profiles.

"Adefovir dipivoxil appears to differ from other anitviral agents being developed for hepatitis B because of its activity against all clinically relevant HBV strains including resistant virus," said Clinical Investigator Teresa L. Wright, MD, Chief of Gastroenterology at the Veterans Administration Medical Center in San Francisco. "We are increasingly facing the issue of viral resistance to currently available anti-HBV medications, particularly in patients who are immuno-compromised. Though we are still defining the clinical consequences of resistance, there is a pressing need for new therapies with activity against these variants when used alone or with other anti-HBV treatments."

Study 437 is a two-year randomized, double-blind, placebo-controlled Phase III trial that will evaluate the safety and efficacy of adefovir dipivoxil at two active doses (10 mg and 30 mg) given once daily. The study is designed to evaluate the treatment effect of adefovir dipivoxil compared to placebo in terms of improvements in liver histology, changes in viral load, rates of seroconversion and other important markers of liver disease. Seroconversion is defined as both the disappearance of the hepatitis B "e" antigen (HBe-antigen), a marker of HBV replication, and the appearance of antibodies specific for this antigen (HBe-antibody).

Data from this Phase III study will be analyzed after the first year of treatment and at trial completion. During the second year of Study 437, researchers will evaluate the long-term safety and resistance profile of adefovir dipivoxil. The potential effect of one versus two consecutive years of treatment with adefovir dipivoxil also will be studied to determine whether withdrawal of active therapy after one year of treatment may increase rates of seroconversion.

Rapid Reduction of HBV DNA, Enhanced Seroconversion

Data from Gilead's Phase II studies in 67 patients demonstrated that 12 weeks of treatment with adefovir dipivoxil at once-daily doses of 5 mg, 30 mg and 60 mg provided potent antiviral activity against the hepatitis B virus. Sixty-seven percent of patients who received a 30 mg daily dose of adefovir dipivoxil exhibited viral suppression that fell below the detectable limits of the branched chain DNA assay. When quantified with a more sensitive assay (PCR), the median reduction of HBV DNA was found to be more than 99.99 percent or 4.0 log10. Similar results were observed in patients with chronic HBV infection and normal blood levels of enzyme markers called hepatic transaminases (ALTs) that indicate liver disease. These results were statistically significant.

Treatment with adefovir dipivoxil also was associated with seroconversion in the group of patients with chronic HBV infection and elevated ALTs. After 24 weeks of follow-up, 27 percent of patients in the 30 mg and 60 mg dose arms lost HBe-antigen, and 20 percent seroconverted. Rates of adverse events and changes in laboratory safety markers were similar in the placebo and treatment groups.

Unique Resistance Profile

To date, researchers have been unable to identify resistant hepatitis B viral isolates associated with adefovir dipivoxil despite

extensive in vitro and in vivo testing. In addition, in vitro studies have demonstrated potent antiviral activity of adefovir dipivoxil against all known lamivudine- and famciclovir-resistant HBV strains, including the common double mutants L528M + M552V and L528M + M552I.

Chronic Hepatitis B: A Major Global Health Problem

Worldwide, there are more than 350 million chronic carriers of HBV, of which approximately one million die each year from complications of the disease, making chronic HBV one of the 10 most common causes of death. In the United States, the disease claims between 4,000 and 5,000 lives annually among the 1.25 million Americans infected with chronic HBV. Complications of chronic HBV include cirrhosis, liver failure and primary liver cancer (hepatocellular carcinoma).

Antiviral Activity in HIV

Adefovir dipivoxil is the active ingredient in PREVEON®, which is being studied in multiple, late-stage clinical trials at different dose levels (120 mg and 60 mg once per day) for the potential treatment of HIV infection. The doses studied for HIV are higher than those being evaluated for the treatment of chronic hepatitis B. During HIV clinical testing, the most common side effects reported with PREVEON have been dose-related gastrointestinal effects, including nausea and loss of appetite. Nephrotoxicity, including changes in serum creatinine and phosphate, is the most important drug-related toxicity. These changes generally occur after six months of treatment, are gradual in onset, asymptomatic, detectable by routine monitoring and resolvable upon dose reduction or withdrawal. Elevations in hepatic transaminases have been observed in some patients.

Gilead Sciences

Gilead Sciences is an independent biopharmaceutical company that seeks to provide accelerated solutions for patients and the people who care for them. The Company discovers, develops and commercializes proprietary therapeutics for important viral diseases, including a currently marketed product for the treatment of CMV retinitis, a sight-threatening viral infection in patients with AIDS. In addition, the Company is developing products to treat diseases caused by HIV, hepatitis B virus and influenza viruses. Gilead common stock is traded on The Nasdaq Stock Market under the symbol GILD.

Editor's note: Patients seeking information about how to participate in the worldwide hepatitis B study may call 1-800-GILEAD-5 or refer to the Clinical Trial Locator on the Gilead Sciences Web site at www.gilead.com.