Gilead Announces Presentation of Data From Phase III Study of Adefovir Dipivoxil in Patients With Precore Mutant Chronic Hepatitis B

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MADRID, Spain, Apr 18, 2002 (BUSINESS WIRE) --

Additional Long-Term Anti-HBV and Resistance Data Presented At 37th Meeting of European Association for the Study of the Liver

Gilead Sciences (Nasdaq:GILD) today announced 48-week data from a Phase III clinical trial (Study 438) of its novel, once-daily, oral antiviral agent adefovir dipivoxil 10 mg that is being developed for the treatment of patients with chronic hepatitis B. Study results show that 48 weeks of treatment with adefovir dipivoxil was associated with improved liver histology and reduced serum hepatitis B virus (HBV) DNA concentration (a marker of viral replication) in patients infected with the precore mutant strain of the virus. In addition, serum HBV DNA concentration was reduced to below the limit of detection (less than 400 copies/mL as measured by Roche Amplicor PCR) in more than half of patients. Precore mutant HBV is a strain of the virus in which a mutation in the viral genome destroys the virus' ability to produce its hallmark "e" antigen. It is more common in Asian and Mediterranean countries, and can be associated with more severe liver disease.

These data were outlined in an oral presentation (#648) given by Stephanos Hadziyannis, MD, Department of Internal Medicine, Hipprokration General Hospital, Athens, Greece at the 37th Annual Meeting of the European Association for the Study of the Liver (EASL) in Madrid, Spain. This presentation is among the more than 20 abstracts at EASL describing the anti-HBV, safety and resistance profile of adefovir dipivoxil in a variety of chronic hepatitis B patient populations. Preliminary data from Study 438 previously were announced in September 2001.

Adefovir dipivoxil belongs to a class of drugs called nucleotide analogues which are designed to work by blocking HBV DNA polymerase, an enzyme involved in the replication of the virus in the body. Gilead recently filed a New Drug Application (NDA) for adefovir dipivoxil with the U.S. Food and Drug Administration (FDA) and a Marketing Authorisation Application (MAA) with the European Medicines Evaluation Agency (EMEA). Gilead has requested a priority, or six month, review in the United States, and anticipates receiving an opinion from the Committee for Propriety Medicinal Products (CPMP) in Europe in the first half of 2003.

"The results presented today demonstrate that treatment with adefovir dipivoxil may potentially alter the course of chronic hepatitis B infections by positively impacting several important clinical markers -- liver histology, serum HBV DNA and ALT levels," said Dr. Hadziyannis. "Patients infected with precore mutant chronic hepatitis B often experience poor clinical outcomes and may exhibit more advanced liver disease. Based on its activity, safety and resistance profile, adefovir dipivoxil offers new hope for potential successful treatment of patients with chronic hepatitis B who are infected with the precore mutant form of the virus."

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About Study 438
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Study 438 is an international, multicenter, double-blind, placebo-controlled Phase III clinical trial that enrolled 185 patients with precore mutant chronic hepatitis B and compensated liver function. The study was conducted in Australia, Canada, France, Greece, Israel, Italy and Southeast Asia. Patients were randomized to receive adefovir dipivoxil 10 mg once daily or placebo for 48 weeks.

Liver biopsies were obtained from 178 patients. Sixty-four percent of patients treated with adefovir dipivoxil exhibited significant improvement in liver histology, compared with 33 percent of patients who received placebo (p=0.0002). Improvement was defined as a greater than or equal to two point reduction in the Knodell HAI score (measuring necro-inflammation -- an inflammatory process in the liver including or leading to death of liver cells) with no concurrent worsening of fibrosis (scarring of liver tissue). Treatment with adefovir dipivoxil also resulted in a median reduction in serum HBV DNA from baseline of 3.91 log10 copies/mL, compared with a median reduction of 1.35 log10 copies/mL (p less than 0.0001) in patients receiving placebo. Serum HBV DNA levels were below the limit of quantification of the assay (less than 400 copies/mL) in 51 percent of the adefovir dipivoxil-treated group, versus zero percent in the placebo group.

Adefovir dipivoxil-treated patients demonstrated a greater median reduction in levels of alanine transaminase (ALT, a measure of

liver damage) than placebo patients (55 IU/L vs. 38 IU/L, p=0.01). In addition, ALT levels normalized in 72 percent of adefovir dipivoxil patients, compared with 29 percent of placebo patients (p less than 0.0001). Over the first 48 weeks of the study, the incidence of adverse events was similar in both the adefovir dipivoxil and placebo groups, and the discontinuation rate was two percent in both groups. The most common adverse events reported were headache, pharyngitis and abdominal pain.

Resistance Surveillance in Studies 437 and 438

The resistance profile of adefovir dipivoxil was characterized in a poster presentation (#577), given by Shelly Xiong, PhD, Gilead, highlighting an integrated resistance analysis of two Phase III clinical trials, studies 437 and 438. Study 437 is a Phase III clinical trial evaluating adefovir dipivoxil 10 and 30 mg monotherapy versus placebo in 515 hepatitis B "e" antigen-positive patients. The week 48 resistance surveillance included 695 chronic hepatitis B patients, 467 of who received adefovir dipivoxil and 228 of who received placebo. Due to undetectable serum HBV DNA at 48 weeks, 197 adefovir dipivoxil-treated patients were not genotyped. Adefovir-associated resistance mutations were not observed in any of the patients evaluated.

"Adefovir possesses specific molecular characteristics intended to raise high genetic barriers to the development of viral resistance," said John C. Martin, PhD, President and CEO, Gilead. "The long-term success of therapy for chronic hepatitis B depends upon the ability of a therapeutic to effectively suppress HBV replication, to do so safely and for a long period of time without giving rise to resistant viral stains. The clinical data presented at this conference suggest that Gilead may have achieved these goals with the development of adefovir dipivoxil."

Activity of Adefovir Dipivoxil Against Different HBV Genotypes

Results of a genotypic substudy of 698 serum samples from patients enrolled in Studies 437 and 438 also will be presented at the conference (#649) by William Delaney, PhD, Gilead. In this analysis, HBV genotypes were determined for all baseline serum samples and the activity of adefovir dipivoxil against all seven HBV genotypes (A-F) was analyzed. After 48 weeks, treatment with adefovir dipivoxil resulted in significant decreases in HBV DNA across all HBV genotypes. Mean reductions in serum HBV DNA by genotype ranged from 3.4 log10 copies/mL to 4.2 log10 copies/mL. The difference in responses among genotypes was not significant (p=0.78), suggesting that adefovir dipivoxil has similar efficacy against all known genotypes of HBV.

Activity of Adefovir Dipivoxil Against cccDNA

Preliminary results evaluating the effect of adefovir dipivoxil treatment on cccDNA (covalently closed circular DNA) in chronic hepatitis B patients with HBeAg+ disease enrolled in Study 437 (substudy, n=20) will be presented by Fabien Zoulim, MD, Inserm Unit 271, Lyon, France (#638). HBV cccDNA is a key intermediate in HBV replication and serves as the template for transcription of viral RNA. Intracellular cccDNA is the reservoir responsible for the persistence of chronic HBV infection. The results from this substudy indicate that treatment with adefovir dipivoxil reduces HBV cccDNA in the liver by 89 percent (n=16) from baseline at 48 weeks, whereas placebo treatment (n=4) showed no reduction (p less than 0.05). These are the first reported results to suggest that antiviral therapy can reduce the virus reservoir in the human liver, the primary target organ for HBV infection.

Long-term Data from Phase II Studies

The resistance profile and prolonged antiviral response of adefovir dipivoxil will be further characterized in a poster presentation (#590) given by Jenny Heathcote, MD, Toronto Western Hospital. The presentation will highlight long-term resistance, efficacy and safety data from the extension phase of Gilead's Study 412. In this Phase II study, 39 patients with chronic hepatitis B who had previously been treated with adefovir dipivoxil 30 mg for greater than or equal to 40 weeks received adefovir dipivoxil 10 mg. Of these patients, 11 had the precore mutant strain of HBV.

In patients treated with adefovir dipivoxil 10 mg beyond 48 weeks, adefovir dipivoxil was associated with a significant median reduction in serum HBV DNA of 3.40 log10 copies/mL (p less than 0.0001) that remained durable through up to nearly two years (3.36 log10 copies/mL at 100 1weeks, p less than 0.0001). Furthermore, by week 100, HBV DNA was undetectable (less than 400 copies/mL) in 70 percent of patients. Median reductions in ALT levels improved from week 48 to week 100 (36 IU/L to 48 IU/L), at which time these levels normalized in 63 percent of patients. In addition, over the course of the study, 21 percent of patients achieved seroconversion, in which the hepatitis B "e" antigen (used to denote HBV replication) disappears and antibodies specific for this antigen appear. Finally, genotypic and phenotypic analyses revealed no adefovir-associated resistance mutations in patients who received 72 to 136 weeks of treatment with adefovir dipivoxil.

"In patients with chronic hepatitis B and evidence of liver inflammation, the long-term suppression of the hepatitis B virus is essential to prevent liver damage and help maintain health," commented Dr. Heathcote. "These data are an important indicator of the potential durability of response to adefovir dipivoxil."

Chronic Hepatitis B

Worldwide, there are approximately 350 million chronic carriers of hepatitis B, of which approximately one million die each year from complications of the disease, making chronic hepatitis B one of the 10 most common causes of death. Complications of chronic hepatitis B include cirrhosis (scarring of the liver), liver failure and primary liver cancer (hepatocellular carcinoma). Between one-quarter and one-third of people with chronic hepatitis B are expected to develop progressive liver disease. Patients infected with the precore mutant strain of hepatitis B may be predisposed to more severe and progressive liver injury. Precore mutant hepatitis B infects up to approximately 50 percent of the 350 million chronic hepatitis B carriers worldwide and is most prevalent in countries of the Mediterranean and Southeast Asia, where between 30-80 percent of chronic hepatitis B patients are estimated to be infected with this strain.

Early Access Program Initiated

In March 2002, Gilead announced the initiation of an early access program in the United States to provide adefovir dipivoxil to chronic hepatitis B patients with lamivudine-resistant HBV. A similar program opened in France in July 2001 and has enrolled 300 patients to date, and additional programs in Canada, Australia and in other countries in Europe will open in the coming months as appropriate regulatory approvals are obtained.

For more information regarding the adefovir dipivoxil early access program, or to request program registration materials, physicians may call 1-800-GILEAD-5 or 1-650-574-3000.

Gilead Sciences

Gilead Sciences is a biopharmaceutical company that discovers, develops and commercializes therapeutics to advance the care of patients suffering from life-threatening diseases worldwide. The company has five marketed products and focuses its research and clinical programs on anti-infectives, including antivirals, antifungals and antibacterials. Headquartered in Foster City, CA, Gilead has operations in the United States, Europe and Australia.

This press release includes forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995, that are subject to risks, uncertainties and other factors that could cause actual results to differ materially from those referred to in the forward-looking statements. Such risks and uncertainties include the risk that further data from ongoing and future clinical trials may not be as favorable as current data and other risks related to regulatory review and approval of adefovir dipivoxil in the United States and Europe. The reader is cautioned not to rely on these forward-looking statements. These and other risks are described in detail in the Gilead Annual Report on Form 10-K for the year ended December 31, 2001 on file with the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Gilead and Gilead assumes no obligation to update any such forward-looking statements.

Note to Editors: For more information on Gilead Sciences, please visit the company's web site at www.gilead.com or call the Gilead Corporate Communications Department at 1-800-GILEAD-5 or 1-650-574-3000.

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