New Data Demonstrate Antiviral Activity of Gilead's Hepsera in Patients with Lamivudine-Resistant Chronic Hepatitis B

November 4, 2002 8:33 AM ET

BOSTON, Nov 4, 2002 (BUSINESS WIRE) --

48-Week Data Presented at 53rd Annual Meeting of the American Association for the Study of Liver Diseases

Gilead Sciences (Nasdaq:GILD) today announced 48-week results from a clinical trial (Study 461) evaluating the antiviral activity and safety of Hepsera(TM) (adefovir dipivoxil 10 mg) when used as monotherapy or in combination with ongoing lamivudine compared to continued lamivudine monotherapy in chronic hepatitis B patients with lamivudine-resistant virus and compensated liver function. Data were presented by Marion Peters, MD, Principal Investigator and Chief of Hepatology Research, University of California, San Francisco Medical Center at the 53rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in Boston, Massachusetts (presentation #845). This presentation is one of ten abstracts at AASLD describing the antiviral activity, safety and resistance profile of Hepsera. The U.S. Food and Drug Administration cleared Hepsera for marketing in September 2002.

Results of the study show that patients with lamivudine-resistant virus who switched to Hepsera monotherapy or added Hepsera to ongoing lamivudine experienced significant virological, biochemical and serological improvements through 48 weeks. Patients receiving Hepsera alone or in combination with lamivudine experienced statistically significant reductions in both serum hepatitis B virus (HBV) DNA and alanine aminotransferase (ALT, a measure of liver damage), compared with patients who received lamivudine only. Patients treated with lamivudine alone did not show significant virological, biochemical or serological benefit compared with their baseline values. The results in the two Hepsera treatment arms shows switching to monotherapy with Hepsera achieved similar results to combination therapy (when Hepsera was added to lamivudine) in patients with lamivudine-resistant HBV.

"These data extend the results seen at 16 weeks through 48 weeks of therapy, indicating that adefovir dipivoxil (Hepsera), whether used alone or in combination with lamivudine, significantly reduces HBV DNA and normalizes ALT levels in chronic hepatitis B patients with lamivudine-resistant virus," said Dr. Peters. "Resistance to lamivudine has been shown to develop in approximately two thirds of patients after four years of therapy. The results of this study are particularly important as physicians consider the best approach to selecting treatment for their patients and for managing those who have developed resistance to lamivudine."

```
Study 461 Design
```

Study 461 is a 48-week randomized, double-blind, active-controlled multicenter study that enrolled 59 patients at sites in the United States, Europe, Australia and Canada. Study participants had chronic hepatitis B with compensated liver function, for which they were being treated with lamivudine monotherapy. At study entry, all patients had developed the YMDD mutation associated with lamivudine resistance and had clinical evidence of resistance to lamivudine with elevated serum HBV DNA and ALT levels. At baseline, patients had a median serum HBV DNA of 8.1 log10 copies/mL (125 million copies/mL).

Patients were randomized (1:1:1) to three study groups receiving 1) Hepsera in combination with placebo, 2) addition of Hepsera in combination with lamivudine 100 mg, or 3) continuation of lamivudine 100 mg in combination with placebo. The primary endpoint for the study was the time-weighted average change from baseline in serum HBV DNA up to 16 weeks of treatment (DAVG16). Secondary end points evaluated the time-weighted average change from baseline in serum HBV DNA up to week 48 (DAVG48) and the change from baseline in serum levels of HBV DNA at 16 and 48 weeks in each treatment arm. Additionally, the study evaluated the proportion of patients whose ALT levels had returned to normal and the proportion of patients with HBeAg loss and HBeAg seroconversion after 48 weeks of treatment.

```
Study 461 Efficacy and Safety Results
```

Through week 48, patients who switched to either Hepsera monotherapy or added Hepsera in combination with lamivudine exhibited statistically significant reductions in median time-weighted change in serum HBV DNA from baseline (DAVG48) of 3.06 log10 copies/mL and 2.93 log10 copies/mL, respectively, compared to an increase of 0.05 log10 copies/mL in patients continuing

on lamivudine monotherapy (p less than 0.001). At week 48, the median decrease from baseline in serum HBV DNA was 4.0 log10 copies/mL and 3.6 log10 copies/mL in patients switching to Hepsera monotherapy and adding Hepsera in combination with lamivudine, respectively, compared to a median change of 0.0 log10 copies/mL for patients continuing on lamivudine monotherapy (p less than 0.001). In addition, ALT levels normalized in 53 percent of patients receiving Hepsera in combination with lamivudine (p less than 0.01) and in 47 percent of patients who switched to Hepsera monotherapy (p less than 0.01) compared to five percent of patients who continued lamivudine monotherapy. Eleven and six percent of patients switching to Hepsera monotherapy and adding Hepsera in combination with lamivudine seroconverted by week 48, respectively, compared to zero percent of patients on lamivudine monotherapy. Seroconversion is defined as both the disappearance of the hepatitis B "e" antigen (HBe-antigen negative), a marker of HBV replication, and the appearance of antibodies specific for this antigen (HBe-antibody positive).

Three patients withdrew from this study; one pre-treatment, one at week 44 due to progression of disease and one due to non-compliance. The most common adverse events reported were asthenia, abdominal pain and pharyngitis, and the frequency and type of adverse events were similar among all treatment arms. Five serious adverse events were reported, none of which were determined to be related to study drug. Through 48 weeks, no patients in this study had elevations in serum creatinine greater than or equal to 0.5 mg/dL from baseline, as confirmed by two consecutive laboratory assessments.

Summary of Results

	Lamivudine (n=19)	Lamivudine+Hepsera (n=20)	Hepsera (n=19)
HBV DNA (log10 copies/mL) DAVG48 (p-value)	0.05	-2.93 (p less than 0.001)	-3.06 (p less than 0.001)
Median change from baseline for serum HBV DNA at week 48 (log10 copies/mL) (p-value)	0.0	-3.6 (p less than 0.001)	-4.0 (p less than 0.001)
Proportion of patients with ALT normalization at week 48 (p-value)	5 percent	53 percent (p less than 0.01)	47 percent (p less than 0.01)
Seroconversion	0 percent	6 percent	11 percent

"The data from this and nine other presentations at AASLD underscore the strength and versatility of Hepsera across a range of patients with varying stages of active liver disease," said John C. Martin, PhD, President and CEO, Gilead Sciences. "We are pleased to be able to share these results -- as well as data from multiple other studies of Hepsera -- to help physicians gain a better understanding of the profile of this important new treatment option."

About Hepsera

Hepsera, administered as an oral 10 mg tablet, is the first nucleotide analogue to receive FDA approval for the treatment of chronic hepatitis B. It was approved in the United States on September 20, 2002. Regulatory review is currently underway in the European Union, Canada and Australia. In clinical trials and expanded access programs, approximately 2,500 patients have been treated with Hepsera for periods of up to three years. The drug works by blocking HBV DNA polymerase, an enzyme involved in the replication of HBV in the body.

In the United States, Hepsera is indicated for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. This indication is based on histological, virological, biochemical and serological responses in adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver function, and in adult patients with clinical evidence of lamivudine-resistant hepatitis B virus with either compensated or decompensated liver function.

Safety Profile

In clinical studies, the discontinuation rates and nature, severity and incidence of side effects and laboratory abnormalities were

similar between people taking Hepsera and those taking placebo through 48 weeks. The most common adverse events observed in these studies were asthenia (weakness), headache, abdominal pain, nausea, flatulence, diarrhea and dyspepsia. These side effects were reported with similar frequency in Hepsera and placebo-treated patients. Through 48 weeks, no patients in the placebo-controlled studies had elevations in serum creatinine greater than or equal to 0.5 mg/dL from baseline. Four percent of patients receiving Hepsera and two percent of patients receiving placebo had increases greater than or equal to 0.3 mg/dL. With extended treatment beyond one year, two of 492 patients (less than one percent) had elevations in serum creatinine greater than or equal to 0.5 mg/dL from baseline and 29 of 492 had elevations greater than or equal to 0.3 mg/dL. These elevations resolved or remained unchanged with either continued treatment or discontinuation.

Additional adverse events reported in pre- and post-liver transplant patients include fever, vomiting, hepatic failure, increases in ALT and AST levels, abnormal liver function, increased cough, pharyngitis, sinusitis, pruritus, rash, increases in serum creatinine, renal failure and renal insufficiency. Thirteen percent of patients (41 of 324) developed an elevation in serum creatinine greater than or equal to 0.5 mg/dL from baseline and 26 percent developed an increase greater than or equal to 0.3 mg/dL through 48 weeks. The contribution of Hepsera to changes in serum creatinine is difficult to assess as the majority of these patients had some degree of underlying renal insufficiency at baseline and other risk factors for renal dysfunction during treatment. These patients should be carefully monitored and may require dose interval adjustments.

As is the case with other antiviral therapies for chronic hepatitis B, physicians need to monitor liver function for exacerbation of hepatitis following discontinuation of therapy. Additionally, HIV resistance may emerge in chronic hepatitis B patients with unrecognized or untreated HIV infection who receive anti-hepatitis B therapies that may have activity against HIV. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals.

About Hepatitis B

Hepatitis B is a serious disease that attacks the liver and can cause chronic (lifelong) infection, cirrhosis of the liver, liver cancer and death in up to a third of patients. In the United States, an estimated 1.25 million people are believed to have chronic hepatitis B, with approximately 100,000 new infections occurring annually. Worldwide, chronic hepatitis B is the leading cause of liver cancer and the tenth leading cause of death (approximately one million people will die this year from complications from the disease).

Hepatitis B is spread through infected blood or body fluids, sexual contact, injection drug use or perinatally from mother to child. Early symptoms include loss of appetite, fever, generalized aches and pains, fatigue, itching, urticaria (hives) and joint pain. Later symptoms may include nausea and vomiting, halitosis (bad breath), dark brown urine, jaundice (yellowing of the skin and eyes) and right-sided abdominal pain (especially with external pressure or palpitation).

About 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 six 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. 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 and in Gilead's Quarterly Reports on Form 10-Q, all of which are 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.

For full prescribing information on Hepsera, please call the Gilead Public Affairs Department at 1-800-GILEAD-5 (1-800-445-3235) or visit www.hepsera.com.

CONTACT: Gilead Sciences
Susan Hubbard, 650/522-5715 (Investors)
Erin Edgley, 650/522-5635 (Media)
http://www.gilead.com

URL: http://www.businesswire.com
Today's News On The Net - Business Wire's full file on the Internet
with Hyperlinks to your home page.