Gilead Sciences Presents 48-Week Phase II Safety and Efficacy Results for Once-Daily Anti-HIV Agent, Tenofovir DF

April 16, 2000 3:42 PM ET

Preliminary Data Presented at ICAR in Baltimore

Foster City, CA -- April 16, 2000

Gilead Sciences, Inc. (Nasdaq: GILD) today announced preliminary results from a Phase II dose-ranging clinical trial (Study 902) evaluating the safety and efficacy of once-daily tenofovir disoproxil fumarate (tenofovir DF) when used to intensify a stable background antiretroviral regimen in 189 treatment-experienced HIV patients. In this study, 48 weeks of treatment with the highest dose of tenofovir DF (300 mg) in 41 anti-retroviral experienced patients was associated with a mean change in HIV RNA of –0.68 $\log_{10}$ copies/mL. The discontinuation rate and incidence of adverse events were similar across all arms of the study. These efficacy and safety results are consistent with those seen at 24 weeks, as previously reported.

These results were presented for the first time on Sunday, April 16, 2000 by clinical investigator Melanie Thompson, MD, Director of the AIDS Research Consortium of Atlanta, during the symposium "Clinical Update on Antiviral Drugs" at the International Conference for Antiviral Research (ICAR) in Baltimore, Maryland.

Study 902 Design

The 48-week double-blind, dose-ranging study enrolled 189 treatment-experienced patients who were on a stable antiretroviral regimen for at least 8 weeks prior to entering the study. Patients were randomized to receive one of three tenofovir DF doses (300 mg, 150 mg or 75 mg) or placebo in addition to their existing treatment regimen. At week 24, all patients receiving placebo were switched in blinded fashion to the tenofovir DF 300 mg treatment arm.

Prior to enrollment, patients had received a mean of 4.6 years of antiretroviral therapy. At baseline, patients had a mean HIV RNA of 3.7 $\log_{10}$ copies/mL and a mean CD4 cell count of 375 cells/mm^3. Baseline genotypic analyses of HIV isolates from 187 of the 189 patients enrolled in the study revealed that 97% had evidence of nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations, 59% had protease inhibitor resistance mutations and 34% had non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations. The high prevalence of mutations associated with the three commonly prescribed classes of antiretrovirals is consistent with the extensive treatment-experience of this study population.

Anti-HIV Activity

In Study 902, anti-HIV activity was observed in all three active treatment arms, with the greatest mean difference from baseline associated with the 300 mg dose of tenofovir DF. The mean change in HIV RNA from baseline for patients receiving the 300 mg dose was –0.68 $\log_{10}$ copies/mL after 48 weeks of treatment (n=41). Patients in the 150 mg and 75 mg tenofovir DF arms had mean changes in viral load of –0.6 $\log_{10}$ copies/mL (n= 34) and –0.43 $\log_{10}$ (n=40), respectively. In addition, patients who had received placebo for the first 24 weeks of the study and switched to the 300 mg dose for the second 24-weeks had a mean change in HIV RNA of –0.71 $\log_{10}$ at 48 weeks (n=19).

"These data demonstrate that tenofovir can have a substantial antiviral effect even in patients with more than four years of previous antiretroviral experience," said Dr. Thompson. "The regimen is simple, and the safety profile to date is very encouraging, suggesting that tenofovir may become an important new option for patients whose alternatives are limited by viral resistance."

Study 902 Safety Results

At 48 weeks, the discontinuation rate in the study was similar across all treatment arms -- 11 patients (20%) in the 300 mg dose group, 12 patients (24%) in the 150 mg dose group, 14 patients (26%) in the 75 mg dose group. At 24 weeks (the placebo-controlled portion of the trial), 7 patients (25%) in the placebo group discontinued; after 24 weeks, all placebo patients who remained on study medication rolled over to the 300 mg dose of tenofovir DF. Additionally, through 48 weeks, no patients

randomized to tenofovir DF 300 mg had confirmed elevations (≥0.5 mg/dL) of serum creatinine (a marker of kidney function).

"We designed Study 902 as a 48-week trial to gain a thorough understanding of the longer-term safety and efficacy profile of tenofovir DF," said John C. Martin, Ph.D., President and Chief Executive Officer of Gilead. "These encouraging results allow us to confidently proceed with the Phase III clinical program for tenofovir DF in a variety of populations, including treatment-naïve patients."

Tenofovir DF 24-Week Resistance Analyses

On Monday, April 17, an oral presentation given by Michael Miller, Ph.D. of Gilead Sciences will further describe the resistance profile of tenofovir DF. This presentation will highlight data from a virology sub-study of all patients enrolled in Study 902. In this sub-study, genotypic analyses of plasma samples from 124 patients were performed at week 24; the remaining patients had insufficient viral load for genotypic analyses.

Of those 124 patients evaluated, the percentage of patients who developed new resistance mutations to background NRTIs, protease inhibitors and NNRTIs was 33% (n=41), 6% (n=8) and 2% (n=3) respectively. The remaining 78 patients had no evidence of new resistance mutations. Only two patients developed the K65R reverse transcriptase mutation, which has been selected by tenofovir DF *in vitro* and by ddI, ddC and abacavir *in vivo*. Neither patient showed evidence of viral rebound at 24 weeks. Because the study was still blinded at the time of data analyses, it is not known whether the patients were on tenofovir DF or placebo, although both patients were taking either abacavir or ddI. These data suggest that after 24 weeks of treatment, there were no novel reverse transcriptase mutations due to therapy with tenofovir DF.

Background on Tenofovir DF for HIV/AIDS

Tenofovir DF is an investigational reverse transcriptase inhibitor in Phase II development for the potential treatment of HIV infection. Tenofovir DF belongs to a new class of drugs called nucleotide analogues, which work by blocking reverse transcriptase, an enzyme crucial to HIV replication. Gilead's preclinical studies have shown that tenofovir is eliminated by the kidney, is not metabolized by the liver and is not associated with cytochrome p450 interactions. Because of the compound's long intracellular half-life, tenofovir DF is currently being evaluated in clinical studies as a single pill taken once daily. In an early clinical study (Study 901), preliminary analysis of data from treatment-naïve patients randomized to receive 300 mg (n=4) of tenofovir DF for 28 days had median reduced plasma HIV RNA levels from baseline of 1.5 $\log_{10}$ copies/mL.

Ongoing Tenofovir DF Phase III Program

To further evaluate the safety and efficacy of tenofovir DF 300 mg in combination with other antiretroviral agents for the treatment of HIV infection, Gilead initiated Phase III clinical testing with Study 907 in November 1999. Underway at the United States, Europe and Australia, Study 907 is enrolling patients who have been on stable antiretroviral therapy of no more than four agents for at least eight weeks. A second 48-week Phase III trial (Study 903) in treatment-naïve patients is anticipated to begin shortly. Patients and physicians who would like more information about enrollment in Studies 903 or 907 may call the AIDS Clinical Trials Information System (ACTIS) at 1-800-TRIALS-A or Gilead Sciences Medical Information at 1-800-GILEAD-5 (1-800-445-3235).

Gilead Sciences

Gilead Sciences, Inc., headquartered in Foster City, CA, is an independent biopharmaceutical company that seeks to provide accelerated solutions for patients and the people who care for them. Gilead discovers, develops, manufactures and commercializes proprietary therapeutics for challenging infectious diseases (viral, fungal and bacterial infections) and cancer. Gilead maintains research, development or manufacturing facilities in Foster City, CA; Boulder, CO; San Dimas, CA; Cambridge, UK and Dublin, Ireland and sales and marketing organizations 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 statements are subject to certain risks and uncertainties, particularly the risk that the safety, efficacy and resistance data observed in Gilead's Phase II clinical trials and preclinical testing may not be observed in Gilead's more reliable Phase III clinical trials and risks related to regulatory approval of tenofovir DF. Actual results could differ materially from those projected in this release. 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, 1999 on file with the U.S. Securities and Exchange Commission.