

## **Gilead's Tenofovir Alafenamide (TAF)-Based Single Tablet HIV Regimen Maintains High Viral Suppression Through 48 Weeks in Phase 2 Study**

September 12, 2013 5:01 PM ET

*-- Efficacy Similar to Stribild<sup>®</sup>, with Favorable Safety Profile --*

DENVER--(BUSINESS WIRE)--Sep. 12, 2013-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced 48-week results from a Phase 2 study (Study 102) evaluating an investigational once-daily single tablet regimen containing tenofovir alafenamide (TAF) for the treatment of HIV-1 infection. At 48 weeks, a regimen of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg was found to be similar to Stribild<sup>®</sup> (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) based on the percentage of patients with HIV RNA levels less than 50 copies/mL, and was associated with more favorable renal and bone safety markers. These findings were presented today in a latebreaker session (Abstract #H-1464d) at the 53<sup>rd</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2013) taking place in Denver.

“These results suggest that TAF has the potential to be an important advance for people living with HIV,” said Paul Sax, MD, Clinical Director of the Division of Infectious Diseases at Brigham and Women’s Hospital, Boston, Professor of Medicine at Harvard Medical School, and an investigator for Study 102. “In this study, the TAF-based regimen matched Stribild’s high viral suppression and demonstrated a favorable safety profile with respect to renal and bone changes.”

In Study 102, 170 HIV-positive treatment-naïve adult patients were randomized (2:1) to receive the investigational TAF-based regimen or Stribild. At 48 weeks, 88.4 percent (n=99/112) of patients taking TAF and 87.9 percent (n=51/58) of patients taking Stribild achieved HIV RNA (viral load) less than 50 copies/mL, based on the FDA snapshot algorithm (intent-to-treat analysis; stratum-adjusted difference between TAF and Stribild: -1.0 percent, p=0.84, 95 percent CI for the difference: -12.1 percent, 10.0 percent). No drug resistance was observed in patients receiving the TAF-based regimen.

Both regimens were generally well tolerated. There were no treatment-related serious adverse events. There were numeric differences in laboratory abnormalities of renal and bone markers, which favored the TAF-based regimen. There was a statistically significant difference in the median change in estimated glomerular filtration rate (eGFR) from baseline to week 48, with eGFR decreasing by -5.5 mL/min in the TAF arm compared to a decline of -10.0 mL/min in the Stribild arm (p=0.041). Additionally, there was a significantly smaller median percentage decrease in bone mineral density from baseline to week 48 for the TAF-based regimen compared to Stribild (-1.00 vs. -3.37 (p<0.001) for the lumbar spine and -0.62 vs. -2.39 (p<0.001) for the hip). There were no pathological bone fractures in either arm of the study.

“Based on these positive results, we believe that TAF has the potential to become a key component of next-generation single tablet regimens in HIV therapy,” said Norbert W. Bischofberger, PhD, Gilead’s Executive Vice President, Research and Development and Chief Scientific Officer. “We are now completing enrollment of two Phase 3 clinical trials comparing a TAF-based regimen to Stribild in patients new to HIV treatment, and look forward to sharing initial results from these large-scale studies by the end of 2014.”

### **About Study 102**

Study 102 is a randomized, double-blind 48-week clinical trial evaluating the efficacy and safety of a once-daily single tablet regimen containing elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg (n=112) compared to Stribild (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) (n=58) among HIV-1 infected treatment-naïve adults with HIV RNA levels greater than or equal to 5,000 copies/mL, CD4 cell counts greater than 50 cells/mm<sup>3</sup> and estimated creatinine clearance of at least 70 mL/min. Bone mineral density was assessed in all patients by DEXA scans at baseline and at 24 and 48 weeks of treatment. The primary endpoint of the study is the percentage of patients with HIV RNA levels less than 50 copies/mL at week 24, per the FDA snapshot algorithm. Secondary endpoints include the proportion of patients who achieve viral load of less than 50 copies/mL at week 48, and changes in HIV-1 RNA and in CD4 cell count from baseline to weeks 24 and 48.

At baseline, patients receiving the TAF-based regimen had a median HIV RNA of 4.55 log<sub>10</sub> copies/mL and median CD4 cell

count of 385 cells/mm<sup>3</sup>. Patients receiving Stribild had a median HIV RNA of 4.58 log<sub>10</sub> copies/mL and median CD4 cell count of 397 cells/mm<sup>3</sup>. At week 48, mean CD4 cell count increases from baseline were 177 cells/mm<sup>3</sup> in the TAF arm and 204 cells/mm<sup>3</sup> for Stribild (p=0.41).

Discontinuations due to adverse events were similar in both treatment arms (3.6 percent for TAF vs. 0 percent for Stribild), and the frequency and nature of adverse events was also similar. The most common adverse events occurring in at least 10 percent of TAF patients were nausea (21 percent for TAF vs. 12 percent for Stribild), diarrhea (16 percent vs. 16 percent), upper respiratory tract infection (15 percent vs. 21 percent), fatigue (14 percent vs. 9 percent), headache (10 percent vs. 14 percent) and cough (10 percent vs. 10 percent).

The incidence of laboratory abnormalities (Grades 3-4) was 25 percent in the TAF arm and 17 percent for Stribild. Grades 3-4 laboratory abnormalities occurring in at least 5 percent of patients in either treatment arm were LDL (low-density lipoprotein or “bad” cholesterol), elevated creatine phosphokinase and neutropenia.

There were no discontinuations due to renal events and no cases of proximal renal tubulopathy in either arm. Additional exploratory markers of proximal renal tubulopathy, measuring impaired absorption and secretion of proteins caused by damage to the proximal tubule, favored the TAF-based regimen. At 48 weeks of treatment, the change from baseline in the ratio of urine retinol binding protein to creatinine for the TAF-based regimen was -0.1 µg/g compared to +20.7 µg/g for Stribild (p=0.001), and the change from baseline in the ratio of urine β-2 microglobulin to creatinine for the TAF-based regimen and Stribild was -33.6 µg/g and +0.4 µg/g, respectively (p=0.008).

Additional information about the study can be found at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **About Tenofovir Alafenamide**

Tenofovir alafenamide (TAF) is a nucleotide reverse transcriptase inhibitor (NtRTI). It is a novel prodrug of tenofovir. Phase 1b dose-ranging studies identified a dose of TAF that is ten times lower than Viread<sup>®</sup> (tenofovir disoproxil fumarate) and provided greater reduction in viral load. The smaller milligram dose of TAF may enable the development of new fixed-dose combinations and single tablet regimens for HIV therapy that are not feasible with Viread.

### **About Elvitegravir**

Elvitegravir is a member of the integrase inhibitor class of antiretroviral compounds. Integrase inhibitors interfere with HIV replication by blocking the ability of the virus to integrate into the genetic material of human cells. Elvitegravir was licensed by Gilead from Japan Tobacco Inc. (JT) in March 2005. Under the terms of Gilead’s agreement with JT, Gilead has exclusive rights to develop and commercialize elvitegravir in all countries of the world, excluding Japan, where JT retains rights.

### **About Cobicistat**

Cobicistat is Gilead’s proprietary potent mechanism-based inhibitor of cytochrome P450 3A (CYP3A), an enzyme that metabolizes drugs in the body. Unlike ritonavir, cobicistat acts only as a pharmacoenhancing or “boosting” agent and has no antiviral activity.

Elvitegravir/cobicistat/emtricitabine/TAF and elvitegravir and cobicistat as single agents are investigational products and their safety and efficacy have not yet been established.

### **Indication and Important Safety Information about Stribild**

Stribild contains four Gilead compounds in a complete once-daily, single tablet regimen: elvitegravir 150 mg; cobicistat 150 mg; emtricitabine 200 mg; and tenofovir disoproxil fumarate 300 mg. Stribild is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve. Stribild does not cure HIV-1 infection.

### **BOXED WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B**

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate (“tenofovir DF”), a component of Stribild, in combination with other antiretrovirals.**
- **Stribild is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of Stribild have not been established in patients coinfecting with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and HIV-1 and have discontinued Emtriva® (emtricitabine) or Viread, which are components of Stribild. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue Stribild. If appropriate, initiation of anti-hepatitis B therapy may be warranted.**

### Contraindications

- **Coadministration:** Do not use with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Do not use with drugs that strongly induce CYP3A as this may lead to a loss of virologic response and possible resistance to Stribild. Use with the following drugs is contraindicated: alfuzosin, rifampin, dihydroergotamine, ergotamine, methylergonovine, cisapride, lovastatin, simvastatin, pimozide, sildenafil for pulmonary arterial hypertension, triazolam, oral midazolam, and St. John’s wort.

### Warnings and Precautions

- **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir DF and Stribild. Monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein in all patients prior to initiating and during therapy; additionally monitor serum phosphorus in patients with or at risk for renal impairment. Cobicistat may cause modest increases in serum creatinine and modest declines in CrCl without affecting renal glomerular function; patients with an increase in serum creatinine greater than 0.4 mg/dL from baseline should be closely monitored for renal safety. Do not initiate Stribild in patients with CrCl below 70 mL/min. Discontinue Stribild if CrCl declines below 50 mL/min. Avoid concurrent or recent use with a nephrotoxic agent.
- **Use with other antiretroviral products:** Stribild should not be coadministered with products containing any of the same active components; with products containing lamivudine; with adefovir dipivoxil; or with products containing ritonavir.
- **Decreases in bone mineral density (BMD)** and cases of osteomalacia have been seen in patients treated with tenofovir DF. Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for bone loss.
- **Fat redistribution and accumulation** have been observed in patients receiving antiretroviral therapy.
- **Immune reconstitution syndrome,** including the occurrence of autoimmune disorders with variable time to onset, has been reported.

### Adverse Reactions

- **Common adverse drug reactions** in clinical studies (incidence greater than or equal to 5%; all grades) were nausea, diarrhea, abnormal dreams, headache and fatigue.

### Drug Interactions

- **CYP3A substrates:** Stribild can alter the concentration of drugs metabolized by CYP3A or CYP2D6.

Do not use with drugs highly dependent on these factors for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening adverse events.

- **CYP3A inducers:** Drugs that induce CYP3A can decrease the concentrations of components of Stribild. Do not use with drugs that strongly induce CYP3A as this may lead to loss of virologic response and possible resistance to Stribild.
- **Antacids:** Separate Stribild and antacid administration by at least 2 hours.
- **Prescribing information:** Consult the full prescribing information for Stribild for more information on potentially significant drug interactions, including clinical comments.

### Dosage and Administration

- **Adult dosage:** One tablet taken orally once daily with food.
- **Renal impairment:** Do not initiate in patients with CrCl below 70 mL/min. Discontinue in patients with CrCl below 50 mL/min.
- **Hepatic impairment:** Not recommended in patients with severe hepatic impairment.

### **Pregnancy and Breastfeeding**

- **Pregnancy Category B:** There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk. An Antiretroviral Pregnancy Registry has been established.
- **Breastfeeding:** Emtricitabine and tenofovir have been detected in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed.

### **About Gilead Sciences**

Gilead Sciences is a biopharmaceutical company that discovers, develops and commercializes innovative therapeutics in areas of unmet medical need. The company's mission is to advance the care of patients suffering from life-threatening diseases worldwide. Headquartered in Foster City, California, Gilead has operations in North America, Europe and Asia Pacific.

### **Forward-Looking Statement**

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, including risks related to the possibility of unfavorable results from other clinical trials involving the single tablet regimen containing TAF, including Phase 3 studies. In addition, Gilead may be unable to complete enrollment of patients in the Phase 3 studies or obtain trial results in the timelines currently anticipated and may need to modify or delay the clinical trials or to perform additional trials. In addition, Gilead may make a strategic decision to discontinue development of the single tablet regimen containing TAF if, for example, Gilead believes commercialization will be difficult relative to other opportunities in its pipeline. Further, Gilead may be unable to obtain approvals from regulatory authorities for the TAF-based single tablet regimen, or for elvitegravir or cobicistat as single agents. If marketing approval is granted for any of these products, there may be significant limitations on their use. As a result, the TAF-based single tablet regimen may never be successfully commercialized. These risks, uncertainties and other factors 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 Gilead's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013, as filed 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.

*U.S. full prescribing information for Stribild and Viread is available at [www.gilead.com](http://www.gilead.com).*

*Stribild and Viread are registered trademarks of Gilead Sciences, Inc.*

*For more information on Gilead Sciences, please visit the company's website at [www.gilead.com](http://www.gilead.com), follow Gilead on Twitter (@GileadSciences) or call Gilead Public Affairs at 1-800-GILEAD-5 or 1-650-574-3000.*

Source: Gilead Sciences, Inc.

Gilead Sciences, Inc.  
Patrick O'Brien, 650-522-1936 (Investors)  
Cara Miller, 650-522-1616 (Media)