Gilead Announces Data Demonstrating Non-Inferiority of Once-Daily Descovy® vs. Once-Daily Truvada® for Prevention of HIV Infection

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– DISCOVER Trial Meets Primary and Secondary Endpoints and Will Support Supplemental Regulatory Filing for Descovy for Pre-Exposure Prophylaxis (PrEP) –

FOSTER CITY, Calif.--(BUSINESS WIRE)--Mar. 6, 2019-- Gilead Sciences, Inc. (NASDAQ: GILD) today announced results from the DISCOVER trial, a two-year Phase 3 randomized, controlled, double-blind study evaluating the safety and efficacy of the investigational use of once-daily Descovy® (emtricitabine 200 mg and tenofovir alafenamide 25mg) for HIV pre-exposure prophylaxis (PrEP), compared with Truvada® (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg), in men who have sex with men and transgender women at risk for sexually acquired HIV infection.

In a late-breaker oral abstract presented today at the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, 5,387 study participants were randomized in a 1:1 ratio and received either Descovy or Truvada. Among the 2,694 participants (4,370 patient-years) who were at risk of HIV-1 infection and received once-daily Descovy, seven HIV infections (HIV incidence 0.16/100 person-years (PY)) were reported. Among the 2,693 participants (4,386 patient-years) who were at risk of HIV-1 infection and received Truvada, 15 HIV infections (0.34/100 PY) were reported. Descovy met the pre-established criteria for non-inferiority to Truvada using a stringent rate ratio statistical comparison, as demonstrated by the upper bound of the 95 percent confidence interval for HIV-1 infection rate ratio being less than the predefined non-inferiority margin of 1.62/100 PY. Additionally, statistically significant advantages with respect to bone and renal laboratory parameters were observed for participants receiving Descovy as compared with those receiving Truvada, which were pre-specified secondary endpoints.

“As the largest HIV prevention trial conducted to date, the DISCOVER trial results clearly demonstrate Descovy for PrEP™ achieved a clinical profile similar to the high efficacy of Truvada and a more favorable bone and renal safety profile,” said John McHutchison, AO, MD, Chief Scientific Officer and Head of Research and Development, Gilead Sciences. “We look forward to filing regulatory applications for Descovy for the PrEP indication as a potential important new option to prevent individuals from becoming infected and contribute to the achievement of national and global HIV prevention goals.”

In the U.S., Descovy is approved in combination with other antiretroviral agents for the treatment of HIV infection in patients weighing ≥ 35 kg and is not indicated for PrEP. Truvada is indicated in combination with safer sex practices for HIV PrEP to reduce the risk of sexually acquired HIV in at-risk adults and adolescents weighing ≥ 35 kg. Descovy and Truvada each have a Boxed Warning in their respective product labels regarding the risk of post-treatment acute exacerbation of hepatitis B; the Truvada label also carries a Boxed Warning for the risk of drug resistance with PrEP in undiagnosed early HIV infection. See below for Important Safety Information and complete Indications.

“The DISCOVER trial enrolled more than 5,000 men who have sex with men and transgender women who were at risk of acquiring HIV in order to gain insights about the efficacy and safety of Descovy and Truvada for PrEP in populations with some of the highest rates of HIV infection,” said Brad Hare, MD, Chief of Infectious Diseases at Kaiser-Permanente, San Francisco. “The very low incidence of HIV in both treatment arms, combined with Descovy’s improved renal and bone safety as compared with Truvada, demonstrate that Descovy for PrEP may help build on the progress made by Truvada, a proven public health tool in the fight against HIV.”

All DISCOVER study participants were adult cis-men who have sex with men or transgender women who had risk of HIV infection through documented high-risk sexual behavior at study entry. Sexually transmitted infection (STI) screening results also demonstrated that participants maintained their sexual risk behavior during the study. Per study protocol, all participants were tested for STIs every three months at three anatomic sites (oropharynx, urethra, rectum), and all received medical treatment and contact tracing as appropriate. Overall, during the study, 57 percent were diagnosed with gonorrhea or chlamydia (from any anatomic site), 42 percent were diagnosed with rectal gonorrhea or rectal chlamydia, and 10 percent were diagnosed with syphilis.

Among the 22 HIV infections reported in the DISCOVER study, five were likely acquired before study entry, 15 occurred in the setting of low or undetectable intracellular drug levels, and two occurred with intermediate or expected intracellular drug levels detected.

Descovy and Truvada were well tolerated and had low discontinuation rates due to adverse events of 1.3 percent and 1.8 percent, respectively. The most common (>15 percent in either group) adverse events were similar in each group and included anal chlamydia, oropharyngeal gonorrhea and rectal gonorrhea.

Study participants randomized to receive Descovy had improved bone and renal safety outcomes relative to those who received Truvada. Bone mineral density (BMD) was tested in a subset of 383 participants. The percent change in spine BMD was reduced by 1.1 percent for those on Truvada while it increased by 0.5 percent in those on Descovy ($p<0.001$) at Week 48. The percent change in hip BMD was reduced by 1.0 percent in those on Truvada while it was increased by 0.2 percent for those on Descovy ($p<0.001$) at Week 48.

All DISCOVER study participants had renal laboratory testing at every visit. The creatinine clearance (estimated glomerular filtration rate) increased by 1.8 mL/min for those randomized to Descovy while it was reduced by 2.3 mL/min in those who received Truvada ($p<0.001$) at Week 48. There were no cases of Fanconi Syndrome in the Descovy arm while one case was reported in the Truvada arm, which led to premature discontinuation of study drug.

The use of Descovy for the prevention of HIV is investigational and has not been determined to be safe or efficacious and is not approved anywhere globally.

IMPORTANT U.S. SAFETY INFORMATION AND INDICATION FOR DESCOVY

BOXED WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- **Descovy is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of Descovy have not been established in patients coinfected with HIV-1 and HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of Descovy. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue Descovy. If appropriate, initiation of anti-hepatitis B therapy may be warranted.**

Warnings and precautions

- Immune reconstitution syndrome, including the occurrence of autoimmune disorders with variable time to onset, has been reported.
- New onset or worsening renal impairment: Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of FTC and tenofovir alafenamide with elvitegravir and cobicistat, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Do not initiate Descovy in patients with estimated creatinine clearance (CrCl) <30 mL/min. Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue Descovy in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.
  Renal monitoring: In all patients, monitor CrCl, urine glucose, and urine protein prior to initiating and during therapy. In patients with chronic kidney disease, additionally monitor serum phosphorus.
- Lactic acidosis and severe hepatomegaly with steatosis: Fatal cases have been reported with the use of nucleoside analogs, including FTC and TDF. Discontinue Descovy if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

Adverse reactions

- Most common adverse reaction (incidence ≥10%; all grades) in clinical studies was nausea (10%).

Drug interactions

- Prescribing information: Consult the full prescribing information for Descovy for more information on potentially significant drug interactions, including clinical comments.
- Metabolism: Drugs that inhibit P-gp can increase the concentrations of components of Descovy. Drugs that induce P-gp can decrease the concentrations of components of Descovy, which may lead to loss of efficacy and development of resistance.
- Drugs affecting renal function: Coadministration of Descovy with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine and tenofovir and the risk of adverse reactions.

Dosage and administration

- Dosage: Patients who weigh ≥25 kg: 1 tablet taken orally once daily with or without food.
- Renal impairment: Not recommended in patients with CrCl <30 mL/min.
- Testing prior to initiation: Test patients for HBV infection and assess CrCl, urine glucose and urine protein.
- Pediatrics: The safety and effectiveness of Descovy coadminstered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

Pregnancy and lactation

- Pregnancy: There is insufficient human data on the use of Descovy during pregnancy. An Antiretroviral Pregnancy Registry (APR) has been established; available data from the APR for FTC shows no difference in the rates of birth defects compared with a U.S. reference population.
- Lactation: Women infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV-1 transmission.

INDICATION

Descovy is indicated in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in patients weighing at least 35 kg.

Descovy is also indicated, in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg.

Limitations of Use:

Descovy is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of acquiring HIV-1 infection.

IMPORTANT U.S. SAFETY INFORMATION AND INDICATION FOR TRUVADA FOR PREP

BOXED WARNING: RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR PrEP IN UNDIAGNOSED EARLY HIV-1 INFECTION and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- **Truvada for PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiation and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of Truvada for PrEP following undetected acute HIV-1 infection. Do not initiate if signs or symptoms of acute HIV-1 infection are present unless HIV-negative status is confirmed**
- **Severe acute exacerbations of hepatitis B have been reported in HBV-infected patients who discontinued Truvada. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients with HBV after discontinuing Truvada. If appropriate, initiation of anti-hepatitis B therapy may be warranted**

Contraindications

- Do not use Truvada for PrEP in individuals with unknown or positive HIV status

Warnings and precautions: Comprehensive risk reduction strategies

- **Reduce HIV-1 risk:** Truvada for PrEP is not always effective in preventing HIV-1. Use only as part of a comprehensive prevention strategy that includes safer sex practices, regular testing for HIV-1 and other STIs, and counseling on reducing sexual risk behaviors
- **Reduce potential for drug resistance:** Truvada for PrEP should only be used in individuals confirmed to be HIV-negative immediately prior to initiation, at least every 3 months while taking Truvada, and upon an STI diagnosis. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only Truvada. Truvada alone is not a complete regimen for treating HIV-1
    - HIV antibody tests may not detect acute HIV infection. If recent exposures are suspected or symptoms of acute HIV infection are present (e.g., fever, fatigue, myalgia, skin rash), delay initiating (≥1 month) or discontinue use and confirm HIV-negative status with a test approved by U.S. Food and Drug Administration (FDA) for the diagnosis of acute HIV infection
    - If a screening test indicates possible HIV-1 infection, convert the HIV-1 PrEP regimen to an HIV treatment regimen until HIV-negative status is confirmed.
- **Counsel on adherence:** Counsel individuals to strictly adhere to their dosing schedule, as efficacy is strongly correlated with adherence. Some individuals, such as adolescents, may benefit from more frequent visits and counseling.

Warnings and precautions

- **New onset or worsening renal impairment:** Cases of acute renal impairment and Fanconi syndrome have been reported with the use of tenofovir disoproxil fumarate (TDF). Truvada is not recommended in individuals with estimated creatinine clearance (CrCl) <60 mL/min. Avoid concurrent or recent use with a nephrotoxic agent. Acute renal failure has been reported after initiation of high dose or multiple NSAIDs in patients at risk for renal dysfunction; consider alternatives to NSAIDs in these patients. Monitor renal function in all patients – See Dosage and Administration
- **Bone effects:** Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia associated with proximal renal tubulopathy, have been reported with the use of TDF Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for bone loss
- **Lactic acidosis and severe hepatomegaly with steatosis:** Fatal cases have been reported with the use of nucleoside analogs, including Truvada. Discontinue use if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations
- **Drug interactions:** See Drug Interactions section. Consider the potential for drug interactions prior to and during use of Truvada and monitor for adverse reactions

Adverse reactions

- **Common adverse reactions** (>2% and more frequently than placebo) of Truvada for PrEP in clinical trials were headache, abdominal pain, and weight loss

Drug interactions

- **Prescribing information:** Consult the full Prescribing Information for Truvada for more information, warnings, and potentially significant drug interactions, including clinical comments
- **Hepatitis C antivirals:** Coadministration with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, or sofosbuvir/velpatasvir /voxilaprevir increases TDF exposure; monitor for adverse reactions
- **Drugs affecting renal function:** Coadministration of Truvada with drugs that reduce renal function or compete for active

tubular secretion may increase concentrations of emtricitabine and/or tenofovir

Pregnancy and lactation

- **Pregnancy:** An Antiretroviral Pregnancy Registry (APR) has been established. Available data from observational studies and the APR show no increase in the rate of major birth defects for Truvada compared with a US reference population. Consider HIV prevention methods, including Truvada for PrEP in at-risk women due to the potential increased risk of HIV-1 infection during pregnancy and mother to child transmission during acute HIV-1 infection
- **Lactation:** Emtricitabine and tenofovir have been detected in human milk. Evaluate the benefits and risks of Truvada for PrEP in breastfeeding women, including the risk of HIV-1 acquisition due to nonadherence, and subsequent mother to child transmission. Health benefits of breastfeeding should be considered along with potential adverse effects of Truvada on the child, which are unknown

Dosage and administration

- **Dosage:** One tablet once daily with or without food
- **HIV screening:** Test for HIV-1 infection prior to initiating and at least every 3 months during treatment
- **HBV screening:** Test for HBV infection prior to or when initiating treatment
- **Renal impairment and monitoring:** Not recommended in individuals with CrCl <60 mL/min. In all patients, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein on a clinically appropriate schedule. In patients with chronic kidney disease, also assess serum phosphorus

INDICATION

Truvada for PrEP (pre-exposure prophylaxis) is indicated to reduce the risk of sexually acquired HIV-1 in adults and adolescents (≥35 kg) who are at risk for HIV, when used in combination with safer sex practices. HIV-negative status must be confirmed immediately prior to initiation

- If clinical symptoms of acute HIV-1 infection are present and recent exposures (<1 month) are suspected, delay initiation for at least 1 month until HIV-negative status is reconfirmed. Alternatively, confirm HIV-negative status with a test cleared by FDA to aid in the diagnosis of acute HIV-1 infection

Individuals at risk for sexually acquired HIV-1 may include those:

- With HIV-1 infected partner(s), or
- Who engage in sexual activity in a high prevalence area or social network and have additional risk factors, such as: inconsistent or no condom use, diagnosis of sexually transmitted infections (STIs), exchange of sex for commodities, use of illicit drugs or alcohol dependence, incarceration, or sexual partners of unknown HIV status with any of these risk factors

About Gilead Sciences

Gilead Sciences, Inc. is a research-based biopharmaceutical company that discovers, develops and commercializes innovative medicines in areas of unmet medical need. The company strives to transform and simplify care for people with life-threatening illnesses around the world. Gilead has operations in more than 35 countries worldwide, with headquarters in Foster City, California.

For nearly 30 years, Gilead has been a leading innovator in the field of HIV, driving advances in treatment, prevention, testing and linkage to care, and cure research. Today, it's estimated that more than 11.5 million people living with HIV globally receive antiretroviral therapy provided by Gilead or one of the company's manufacturing partners.

For more information on Gilead Sciences, please visit the company's website at www.gilead.com.

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 the risk that regulatory authorities, including FDA, may not approve Descovy for PrEP in the currently anticipated timelines or at all, and any marketing approvals, if granted, may have significant limitations on their use. As a result, Descovy for PrEP 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 Annual Report on Form 10-K for the year ended December 31, 2018, 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 Descovy and Truvada, including **BOXED WARNING**, is available at www.gilead.com.*

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

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