Gilead's Odefsey® (Emtricitabine, Rilpivirine, Tenofovir Alafenamide) Meets Primary 48-Week Objective in Two Phase 3b Studies

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FOSTER CITY, Calif.--(BUSINESS WIRE)--Jul. 21, 2016-- Gilead Sciences, Inc. (Nasdaq:GILD) today announced that two Phase 3b switch studies evaluating Odefsey® (emtricitabine 200mg/rilpivirine 25mg/tenofovir alafenamide 25mg) for the treatment of HIV-1 infection met their primary objectives. The ongoing studies were designed to explore the efficacy and safety of Odefsey among virologically suppressed adult patients switching from the tenofovir disoproxil fumarate (TDF)-based regimens Complera® (emtricitabine 200mg/rilpivirine 25mg/tenofovir disoproxil fumarate 300mg) (Study 1216) or Atripla® (efavirenz 600mg/emtricitabine 200mg/tenofovir disoproxil fumarate 300mg) (Study 1160). Odefsey combines Gilead's emtricitabine and tenofovir alafenamide with rilpivirine, marketed by Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Odefsey maintained similar rates of virologic suppression as the TDF-based regimens in both studies based on the proportion of patients with HIV-1 RNA levels (viral load) <50 copies/mL. At Week 48, virologic suppression was maintained in 94 percent of patients taking Odefsey and in 94 percent of patients taking Complera in Study 1216 (difference: -0.3 percent; 95 percent CI: -4.2 percent to +3.7 percent), and in 90 percent of patients taking Odefsey versus 92 percent of patients taking Atripla in Study 1160 (difference: -2.0 percent; 95 percent CI: -5.9 percent to +1.8 percent).

Compared to the TDF-based regimens, Odefsey demonstrated statistically significant improvements in bone mineral density (BMD) at the hip and spine ($p<0.001$) in both studies. Additionally, improvements in total and tubular proteinuria statistically favored Odefsey in both studies ($p<0.001$). Study regimens were generally well tolerated, and general safety and discontinuation rates due to adverse events were comparable in the two studies. The most commonly reported adverse events for Odefsey included upper respiratory tract infection, diarrhea, nasopharyngitis, cough and headache. Gilead plans to submit these data for presentation at scientific conferences in 2016.

"As people are living longer with HIV, there is an increasing need for safe and tolerable treatment options to help address the long-term health needs of people living with HIV," said Norbert Bischofberger, PhD, Executive Vice President, Research and Development and Chief Scientific Officer, Gilead Sciences. "Results from these two studies support the efficacy, as well as the renal and bone safety profile, of Odefsey as a new treatment option for virologically suppressed patients."

Odefsey was approved in the United States on March 1, 2016, and is indicated as a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and older who have no antiretroviral treatment history and HIV-1 RNA levels ≤100,000 copies/mL. Odefsey is also indicated as replacement for a stable antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) for at least six months with no history of treatment failure and no known resistance to the individual components of Odefsey. No dosage adjustment of Odefsey is required in patients with estimated creatinine clearance ≥30 mL per minute.

Odefsey has a boxed warning in its product label regarding the risks of lactic acidosis/severe hepatomegaly with steatosis, and post treatment acute exacerbation of hepatitis B. See below for important safety information.

About Studies 1216 and 1160

Study 1216 is a Phase 3b, randomized, double-blind, multicenter study among 630 virologically suppressed adults (HIV-1 RNA levels <50 copies/mL) on a stable regimen of Complera for ≥ six consecutive months. Patients were randomized 1:1 to either maintain their Complera regimen or switch to Odefsey. Study 1160 is a Phase 3b, randomized, double-blind, multicenter study among 875 virologically suppressed adults (HIV-1 RNA levels <50 copies/mL) on a stable regimen of Atripla for ≥ six consecutive months. Patients were randomized 1:1 to either maintain their Atripla regimen or switch to Odefsey. The studies will follow patients for 96 weeks after randomization.

The studies are ongoing. The primary objective of each study is to evaluate the efficacy of switching from Complera or Atripla to Odefsey in HIV-1 positive subjects who are virologically suppressed as determined by the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 as defined by the FDA snapshot algorithm. The secondary objectives are to evaluate the bone safety of the regimens by the percent change from baseline in hip and spine BMD at Week 48 and Week 96, to evaluate the safety and tolerability of the treatment arms through Week 48 and to evaluate the efficacy, safety and tolerability of the treatment arms through Week 96.

Additional information about the studies can be found at www.clinicaltrials.gov.

Important U.S. Safety Information for Odefsey

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 in combination with other antiretrovirals.**
- **Odefsey is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of Odefsey 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 and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of Odefsey. 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 Odefsey. If appropriate, initiation of anti-hepatitis B therapy may be warranted.**

Contraindications

- **Coadministration:** Do not use with drugs that induce CYP3A or increase gastric pH as this may lead to loss of efficacy and possible resistance to Odefsey or the NNRTI class. Do not use with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, proton pump inhibitors (e.g., dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole), systemic dexamethasone (>1 dose) and St. John's wort.

Warnings and precautions

- **Skin and hypersensitivity reactions:** Severe skin and hypersensitivity reactions have been reported with the use of rilpivirine-containing regimens, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). In rilpivirine clinical trials, most rashes were Grades 1-2 and occurred in the first 4-6 weeks of treatment; Grades 2-4 rash occurred in 1% of subjects. Discontinue Odefsey immediately if severe skin or hypersensitivity reactions occur, including severe rash or rash accompanied by fever, blisters, mucosal involvement, conjunctivitis, facial edema, angioedema, hepatitis or eosinophilia. Monitor clinical status including laboratory parameters and initiate appropriate therapy.
- **Loss of virologic response due to drug interactions:** See Contraindications and Drug Interactions sections. Consider the potential for drug interactions prior to and during Odefsey therapy and monitor for adverse reactions.
- **Prolongation of QTc interval:** Rilpivirine doses 3 and 12 times higher than the recommended dose can prolong the QTc interval. Consider alternatives to Odefsey in patients at higher risk for Torsade de Pointes or when coadministered with a drug with known risk of Torsade de Pointes.
- **Depressive disorders:** Evaluate patients with severe depressive symptoms to assess if symptoms are due to Odefsey and if the risks of continued treatment outweigh the benefits. In rilpivirine adult clinical trials (N=686), the incidence of depressive disorders was 9%, Grades 3-4 depressive disorders was 1%, discontinuation due to depressive disorders was 1%, and suicidal ideation and suicide attempt was reported in 4 and 2 subjects, respectively. In a rilpivirine adolescent clinical trial (N=36), the incidence of depressive disorders was 19%, Grades 3-4 depressive disorders was 6%, and suicidal ideation and suicide attempt were reported in 1 subject.
- **Hepatotoxicity:** Hepatic adverse events have been reported, including cases of hepatic toxicity, in patients without

pre-existing hepatic disease or other identifiable risk factors. In patients with hepatic abnormalities (e.g., hepatitis, elevated liver-associated tests), order laboratory tests before starting treatment and monitor for hepatotoxicity during treatment; consider testing and monitoring in all patients.

- **Fat redistribution** or accumulation has been observed in patients receiving antiretroviral therapy.
- **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 emtricitabine and tenofovir alafenamide with elvitegravir and cobicistat, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Do not initiate Odefsey 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 Odefsey 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.

- **Bone loss and mineralization defects:** Decreases in bone mineral density (BMD) have been reported with the use of tenofovir prodrugs. Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for bone loss. Mineralization defects, including osteomalacia associated with PRT, have been reported with the use of TDF-containing products.

Adverse reactions

- **Most common adverse reactions** with rilpivirine (incidence ≥2%, Grades 2-4) are depressive disorders (2%), insomnia (2%) and headache (2%); and with emtricitabine and tenofovir alafenamide (incidence ≥10%, all grades) is nausea (10%).

Drug interactions

- **Prescribing information:** Consult the full prescribing information for Odefsey for more information on Contraindications, Warnings, and potentially significant drug interactions, including clinical comments.
- **Metabolism:** Drugs that induce CYP3A or P-gp and drugs that increase gastric pH can decrease the concentrations of components of Odefsey. Drugs that inhibit CYP3A or P-gp can increase the concentrations of components of Odefsey.
- **QT prolonging drugs:** Consider alternatives to Odefsey in patients taking a drug with known risk of Torsade de Pointes.
- **Drugs affecting renal function:** Coadministration of Odefsey 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 12 years and older (≥35 kg): 1 tablet taken orally once daily with a meal.
- **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.
- **Testing after initiation:** In virologically-suppressed patients, additional monitoring of HIV-1 RNA and regimen tolerability is recommended.

Pregnancy and lactation

- **Pregnancy:** There are insufficient data on the use of Odefsey during pregnancy. In animal studies, no adverse developmental effects were observed with the components of Odefsey. An Antiretroviral Pregnancy Registry has

been established.

- **Lactation:** Women infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV-1 transmission.

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. Gilead has operations in more than 30 countries worldwide, with headquarters in Foster City, California.

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 physicians may not see the benefits of prescribing Odefsey. 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 March 31, 2016, 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, including **BOXED WARNINGS**, for Atripla, Complera and Odefsey are 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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