PRODUCT NAME

ODEFSEY® FILM-COATED TABLET 200MG/25MG/25MG
(emtricitabine/rilpivirine/tenofovir alafenamide)

DOSAGE FORMS AND STRENGTHS

Dosage Form	Gray, capsule-shaped, film-coated tablets debossed with "GSI" on one side and "255" on the other side of the tablet.
Strength	Each tablet contains 200 mg of emtricitabine, 25 mg of rilpivirine (equivalent to 27.5 mg of rilpivirine hydrochloride), and 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate).

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

ODEFSEY® is indicated as a complete regimen for the treatment of human immunodeficiency virus type-1 (HIV-1) infection in adults and pediatric patients (12 years of age and older with body weight at least 35 kg) with a viral load ≤ 100,000 HIV-1 RNA copies/mL at the start of therapy, and without known mutations associated with resistance to any of the three antiretroviral components. (see *Pharmacological Properties - Clinical Studies*).

Dosage and Administration

Adults and Pediatric Patients 12 to less than 18 years of age and weighing ≥35 kg

The recommended dose of ODEFSEY® is one tablet taken orally once daily with food (see *Pharmacological Properties - Pharmacokinetic Properties*).

If the patient misses a dose of ODEFSEY® within 12 hours of the time it is usually taken, the patient should take ODEFSEY® with food as soon as possible and resume the normal dosing schedule. If a patient misses a dose of ODEFSEY® by more than 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 4 hours of taking ODEFSEY® another tablet should be taken with food. If a patient vomits more than 4 hours after taking ODEFSEY® they do not need to take another dose of ODEFSEY® until the next regularly scheduled dose.

Special populations

Pediatrics (less than 12 years of age)

The safety and efficacy of ODEFSEY® have not been established in pediatric patients less than 12 years of age or weighing < 35 kg.

Elderly (65 years of age and older)

No data are available on which to make a dose recommendation for patients over the age of 65 years.

Renal impairment

No dose adjustment of ODEFSEY® is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL/minute.

ODEFSEY® should not be initiated in patients with estimated creatinine clearance below 30 mL/minute as there are insufficient data available regarding the use of ODEFSEY® in this population.

No data are available to make dose recommendations in pediatric patients with renal impairment.

Hepatic impairment

No dose adjustment of ODEFSEY® is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. ODEFSEY® has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Hence, ODEFSEY® is not recommended for use in patients with severe hepatic impairment. (see *Pharmacological Properties Pharmacokinetic Properties*).

Contraindications

Known hypersensitivity to emtricitabine (FTC), rilpivirine (RPV), tenofovir alafenamide (TAF), or to any of the excipients.

ODEFSEY® should not be coadministered with the following medicinal products, as significant decreases in RPV plasma concentrations may occur (due to CYP3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of ODEFSEY® (see *Interactions*):

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifampin, rifapentine
- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole
- the glucocorticoid systemic dexamethasone, except as a single dose treatment
- St. John's wort (*Hypericum perforatum*)

Warnings and Precautions

HIV and hepatitis B virus (HBV) co-infection

The safety and efficacy of ODEFSEY® have not been established in patients coinfected with HIV-1 and HBV. Discontinuation of ODEFSEY® therapy in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC or TAF components of ODEFSEY®. Patients coinfected with HIV-1 and HBV who discontinue

ODEFSEY® should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Coadministration with other drugs

ODEFSEY® should not be administered concurrently with other medicinal products containing the same active components FTC, RPV or TAF, or with medicinal products containing lamivudine, TDF, or with adefovir dipivoxil. Caution should be given to prescribing ODEFSEY® with medicinal products that may reduce the exposure of RPV (see *Contraindications* and *Interactions*).

Immune reconstitution inflammatory syndrome

In HIV-infected patients treated with combination antiretroviral therapy, including with FTC, immune reconstitution syndrome has been reported. In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of antiretroviral therapy. Relevant examples include cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of elvitegravir (EVG) + cobicistat (COBI) + emtricitabine (FTC) + tenofovir alafenamide fumarate (TAF), there have been no cases of Fanconi syndrome or proximal renal tubulopathy. Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Interactions

As ODEFSEY® contains FTC, RPV, and TAF, any interactions that have been identified with these agents individually may occur with ODEFSEY®.

<u>Emtricitabine</u>

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low. Co-administration of emtricitabine with medicinal products that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the co-administered medicinal product. Medicinal products that decrease renal function may increase concentrations of emtricitabine.

Drugs Inducing or Inhibiting CYP3A Enzymes

RPV is primarily metabolized by cytochrome P450 (CYP) 3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of RPV.

Coadministration of RPV and drugs that induce CYP3A resulted in decreased plasma concentrations of RPV, which could potentially reduce the therapeutic effect of ODEFSEY® (see Table 1 for drugs studied). Other drugs inducing CYP3A enzymes include carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifapentine, rifampin, dexamethasone, and St. John's wort (*Hypericum perforatum*).

Coadministration of RPV and drugs that inhibit CYP3A resulted in increased plasma concentrations of RPV (see Table 1 for drugs studied).

Drugs Inducing or Inhibiting P-gp

TAF, a component of ODEFSEY®, is transported by P glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Table 1). Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of ODEFSEY® and development of resistance. Coadministration of ODEFSEY® with drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF.

Drugs Increasing Gastric pH

Coadministration of RPV with drugs that increase gastric pH (such as proton pump inhibitors, H_2-receptor antagonists, and antacids) may decrease plasma concentrations of RPV, which could potentially reduce the therapeutic effect of ODEFSEY® (see Table 1 for drugs studied).

QT Prolonging Drugs

There is limited information available on the potential for a pharmacodynamic interaction between RPV and drugs that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of RPV (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram. ODEFSEY® should be used with caution when coadministered with a drug with a known risk of *Torsade de Pointes*.

Established and Other Potentially Significant Drug Interactions

ODEFSEY® is indicated for use as a complete regimen for the treatment of HIV-1 infection and should not be coadministered with other antiretroviral products. Therefore, information regarding drug-drug interactions with other antiretroviral products is not provided. Drug interaction information for ODEFSEY® with potential concomitant drugs is summarized in Table 1. The

drug interactions described are based on studies conducted with ODEFSEY® or the components of ODEFSEY® (FTC, RPV and TAF) as individual agents, or are potential drug interactions that may occur with ODEFSEY®.

The table is not all-inclusive (see also Pharmacological Properties: Pharmacokinetics Properties: Assessment of Drug Interactions, Table 12 – Table 15) (see *Contraindications*).

Table 1. Established and Other Potentially Significant Drug Interactions		
Concomitant Drug Class: Drug Name	**Effect[a]**	**Clinical Comment**
Other Agents		
Azole Antifungal Agents: itraconazole ketoconazole[b]	↑ rilpivirine ↓ ketoconazole ↑ tenofovir alafenamide	Concomitant use of ODEFSEY® with azole antifungal agents (CYP3A and P-gp inhibitors) may cause an increase in the plasma concentrations of RPV and TAF. No dose adjustment is required when ODEFSEY® is coadministered with azole antifungal agents.
Antimycobacterials: rifabutin rifampin[b] rifapentine	↓ rilpivirine ↓ tenofovir alafenamide	Concomitant use of ODEFSEY® with rifampin, rifabutin, and rifapentine (potent CYP3A and P-gp inducers) may cause significant decreases in RPV and TAF plasma concentrations. This may result in loss of therapeutic effect of ODEFSEY®. Coadministration of ODEFSEY® with rifabutin is not recommended. Coadministration of ODEFSEY® with rifampin and rifapentine is contraindicated.
H_2-Receptor Antagonists: famotidine[b]	↔ rilpivirine (famotidine taken 12 hours before rilpivirine) ↓ rilpivirine (famotidine taken 2 hours before rilpivirine) ↔ rilpivirine (famotidine taken 4 hours after rilpivirine)	The combination of ODEFSEY® and H_2-receptor antagonists should be used with caution as coadministration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). H_2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after ODEFSEY®.
Hepatitis C Virus Antiviral Agents: boceprevir telaprevir	Effect on boceprevir, telaprevir, or tenofovir alafenamide concentrations unknown	Coadministration with boceprevir or telaprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of TAF based on *in vitro* data. Coadministration of ODEFSEY® and boceprevir or telaprevir is not recommended.
Narcotic Analgesics: methadone	↓ R (–) methadone ↓ S (+) methadone	No dose adjustments are required when initiating coadministration of methadone with ODEFSEY®. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.

[a] ↑ =increase, ↓=decrease, ↔=no effect

[b] This interaction study has been performed with a dose (150 mg of RPV) higher than the recommended dose for RPV assessing the maximal effect on the coadministered drug. The dosing recommendation is applicable to the recommended dose of RPV 25 mg once daily.

Drugs without clinically significant interactions

Based on drug interaction studies conducted with the components of ODEFSEY®, no clinically significant drug interactions have been either observed or expected when ODEFSEY® is combined with the following drugs: acetaminophen, atorvastatin, buprenorphine, digoxin, famciclovir, ledipasvir/sofosbuvir, metformin, midazolam, naloxone, norbuprenorphine,

norethindrone, norgestimate/ethinyl estradiol, sildenafil, simeprevir, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir.

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no adequate and well-controlled studies of ODEFSEY® or its components in pregnant women. ODEFSEY® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Emtricitabine

Reproductive studies were conducted in rats, mice, and rabbits. Animal studies (performed at 60- to 120-fold human exposure) did not indicate harmful effects of FTC with respect to fertility, pregnancy, fetal parameters, parturition, or postnatal development.

Rilpivirine

Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. There was no teratogenicity with RPV in rats and rabbits. The exposures at the embryo fetal No Observed Adverse Effect Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg RPV once daily [see *Non-clinical Information*].

No human data on the effect of RPV on fertility are available. In a study conducted in rats, there were no effects on mating or fertility with RPV up to 400 mg/kg/day, a dose of RPV that showed maternal toxicity [see *Non-clinical Information*]. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg RPV once daily.

Lower exposures of rilpivirine were observed during pregnancy; therefore, viral load should be monitored closely.

Rilpivirine in combination with a background regimen was evaluated in a clinical trial of 19 pregnant women during the second and third trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to rilpivirine as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6-12 weeks). Virologic response was preserved throughout the trial period. No mother to child transmission occurred in all 10 infants born to the mothers who completed the trial and for whom the HIV status was available. Rilpivirine was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of rilpivirine in HIV-1 infected adults (see *Pharmacokinetic Properties-Special Populations – Pregnancy and Postpartum*).

Tenofovir Alafenamide

Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with TAF during pregnancy, there were no toxicologically significant effects on developmental endpoints.

Breast-feeding

There is insufficient information on the effects of all the components of ODEFSEY® in newborns/infants, therefore ODEFSEY® should not be used during breast-feeding.

Emtricitabine

In humans, samples of breast milk obtained from five HIV-1 infected mothers given FTC/TDF show that FTC is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the FTC IC_{50} but 3 to 12 times lower than the C_{min} achieved from oral administration of FTC. Breastfeeding infants whose mothers are being treated with FTC may be at risk for developing viral resistance to FTC. Other FTC-associated risks in infants breastfed by mothers being treated with FTC are unknown.

Rilpivirine

It is not known whether RPV is secreted in human milk.

Tenofovir Alafenamide

In animal studies it has been shown that tenofovir is secreted into milk. It is not known whether TAF is secreted in human milk.

Women of childbearing potential/contraception in males and females

The use of ODEFSEY® should be accompanied by the use of effective contraception.

Effects on Ability to Drive and Use Machines

Patients should be informed that fatigue, dizziness and somnolence have been reported during treatment with the components of ODEFSEY® (see *Adverse Reactions*). This should be considered when assessing a patient's ability to drive or operate machinery.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of FTC/RPV/TAF based on the comprehensive assessment of the available adverse event information. A causal relationship with FTC/RPV/TAF cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ODEFSEY® is based on studies of FTC+TAF when given with elvitegravir (EVG) + cobicistat (COBI) as the fixed-dose combination tablet; studies of RPV when given with FTC+TDF as individual components or as the fixed-dose combination tablet, FTC/RPV/TDF; and studies of ODEFSEY®.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥10%), common (≥1% and <10%), or uncommon (≥0.1% and <1%).

Emtricitabine+Tenofovir Alafenamide-Containing Regimens

Experience from Clinical Studies in Treatment-Naïve Patients

Assessment of adverse reactions is based on pooled data from two 144-week controlled clinical studies (GS-US-292-0104 and GS-US-292-0111) in which 1733 treatment-naïve patients received FTC+TAF (N=866) or FTC+TDF (N=867), both given with EVG+COBI as a fixed-dose combination tablet.

NERVOUS SYSTEM DISORDERS
Very common: headache

GASTROINTESTINAL SYSTEM DISORDERS
Very common: diarrhea, nausea
Common: vomiting, abdominal pain, dyspepsia, flatulence

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Common: rash

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Very Common: fatigue

Experience from Clinical Studies in Virologically Suppressed Patients

No new adverse reactions to FTC+TAF were identified through Week 48 in an open-label clinical study (GS-US-292-0109) of virologically suppressed patients who switched treatment from a TDF-containing combination regimen to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet (N=959).

Experience from Clinical Studies in Patients with Renal Impairment

The safety of FTC+TAF was evaluated through Week 144 in an open-label clinical study (GS-US-292-0112), in which 248 HIV-1 infected patients who were either treatment-naïve (N=6) or virologically suppressed (N=242) with mild to moderate renal impairment (eGFR by Cockcroft-Gault method 30−69 mL/min) received FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. The safety profile of FTC+TAF in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (see *Clinical Studies*).

Experience from Clinical Studies in Pediatric Patients

The safety of FTC+TAF was evaluated through Week 48 in an open-label clinical study (GS-US-292-0106) in which 50 HIV-1 infected, treatment-naïve pediatric patients aged 12 to <18 years received FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. In this study, the safety profile of FTC+TAF in adolescent patients was similar to that in adults.

Rilpivirine-Containing Regimens

Experience from Clinical Studies in Treatment-Naïve Patient

Adult Patients

The safety assessment is based on the Week 96 pooled data from 1368 patients in the controlled studies TMC278-C209 and TMC278-C215 in antiretroviral treatment-naïve HIV-1 infected adult patients, 686 of whom received RPV 25 mg once daily in combination with other antiretroviral medicinal products. The median duration of exposure for patients in the RPV arm was 104 weeks. No new adverse reaction terms were identified between 48 weeks and 96 weeks. Frequencies of adverse reactions are based on Grade 2 to 4 treatment-emergent adverse events and Grade 3 to 4 laboratory abnormalities.

IMMUNE SYSTEM DISORDERS
Uncommon: immune reconstitution syndrome

METABOLISM AND NUTRITION DISORDERS
Common: decreased appetite

PSYCHIATRIC DISORDERS
Common: depression, insomnia, abnormal dreams, sleep disorders
Uncommon: depressed mood

NERVOUS SYSTEM DISORDERS
Common: headache, dizziness
Uncommon: somnolence

GASTROINTESTINAL DISORDERS
Common: abdominal pain, nausea, vomiting
Uncommon: abdominal discomfort

HEPATOBILIARY DISORDERS
Common: transaminases increased

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Common: rash

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Common: fatigue

Patients Coinfected with Hepatitis B and/or Hepatitis C Virus

In patients coinfected with hepatitis B or C virus receiving RPV, the incidence of hepatic enzyme elevation was higher than in patients receiving RPV who were not coinfected. The pharmacokinetic exposure of RPV in coinfected patients was comparable to that in patients without coinfection.

Experience from Clinical Studies in Pediatric Patients

The safety assessment is based on Week 48 data from one single-arm, open-label study (Study TMC278-C213) in 36 pediatric patients 12 to less than 18 years of age and weighing at least 32 kg. No patients discontinued treatment due to adverse reactions. No new adverse reactions were identified compared to those seen in adults.

Most adverse reactions were Grade 1 or 2. Adverse reactions (all grades) of Very Common frequency were headache, depression, somnolence, and nausea. No Grade 3 to 4 laboratory abnormalities for AST/ALT or Grade 3 to 4 adverse reactions of transaminase increased were reported.

ODEFSEY®

Experience from Clinical Studies in Virologically Suppressed Patients

No new adverse reactions to ODEFSEY® were identified through Week 96 in clinical trials of virologically suppressed patients who switched from FTC/RPV/TDF to ODEFSEY® (GS-US-366-1216, N=316), or from efavirenz [EFV]/FTC/TDF to ODEFSEY® (GS-US-366-1160, N=438).

Postmarketing Experience

In addition to adverse reaction reports from clinical studies the following adverse reactions have also been identified during postapproval use of FTC/RPV/TDF. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

METABOLISM AND NUTRITION DISORDERS
Weight increased

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Severe skin reactions with systemic symptoms have been reported during postmarketing experience, including rashes accompanied by fever, blisters, conjunctivitis, angioedema, elevated liver function tests, and/or eosinophilia.

The following adverse reactions have been identified during postapproval use of products containing TAF:

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Angioedema, urticaria

Overdose

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with ODEFSEY® consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient.

Emtricitabine

FTC can be removed by hemodialysis, which removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing.

It is not known whether FTC can be removed by peritoneal dialysis.

Rilpivirine

There is no specific antidote for overdose with RPV. Human experience of overdose with RPV is limited. Since RPV is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

Tenofovir Alafenamide

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR19.

Mechanism of action

Emtricitabine

FTC is a nucleoside analogue of 2'-deoxycytidine. FTC is phosphorylated by cellular enzymes to form FTC triphosphate. FTC triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

FTC has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

FTC triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Rilpivirine

RPV is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor of HIV-1. RPV activity is mediated by noncompetitive inhibition of HIV-1 reverse transcriptase. RPV does not inhibit the human cellular DNA polymerase α, β, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide

TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). TAF is permeable into cells, and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than TDF in loading tenofovir into

peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus. *In vitro* studies have shown that both FTC and tenofovir can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ, and there is no evidence of mitochondrial toxicity *in vitro* based on several assays including mitochondrial DNA analyses.

Pharmacodynamic effects

Microbiology

Antiviral Activity

Emtricitabine

The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC_{50}) values for FTC were in the range of 0.0013 to 0.64 μM.

FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μM).

In two-drug combination studies of FTC with NRTIs (abacavir, didanosine, lamivudine, stavudine, tenofovir, and zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine, and RPV), protease inhibitors (PIs) (amprenavir, nelfinavir, ritonavir, and saquinavir), and the integrase strand transfer inhibitor EVG, additive to synergistic effects were observed. No antagonism was observed for these combinations.

Rilpivirine

RPV exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM (0.27 ng/mL). Although RPV demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2510 to 10830 nM (920 to 3970 ng/mL), treatment of HIV-2 infection with RPV is not recommended in the absence of clinical data.

RPV demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/mL) and group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/mL).

RPV showed additive to synergistic antiviral activity in combination with the N(t)RTIs (abacavir, didanosine, FTC, lamivudine, stavudine, tenofovir and zidovudine); the PIs (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir); the NNRTIs (efavirenz, etravirine, and nevirapine); the fusion inhibitor enfuvirtide; the entry inhibitor maraviroc; and the integrase inhibitor raltegravir.

Tenofovir Alafenamide

The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4-T lymphocytes. The EC_{50} values for TAF were in the range of 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain- specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs), additive to synergistic effects were observed. No antagonism was observed for these combinations.

Resistance

In Cell Culture

Emtricitabine

HIV-1 isolates with reduced susceptibility to FTC have been selected in cell culture. Reduced susceptibility to FTC was associated with M184V/I mutations in HIV-1 RT.

Rilpivirine

RPV-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI-resistant HIV-1. The most commonly observed amino acid substitutions that emerged included: L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C, and M230I.

Tenofovir Alafenamide

HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed. HIV-1 isolates with the K65R mutation have low-level reduced susceptibility to abacavir, FTC, tenofovir, and lamivudine. *In vitro* drug resistance selection studies with TAF have shown no development of high-level resistance after extended culture.

In Treatment-Naïve Adult Patients

Emtricitabine and Tenofovir Alafenamide

In a pooled analysis of antiretroviral-naïve patients receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet in Phase 3 studies GS-US-292-0104, and GS-US-292-0111,

genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA ≥400 copies/mL at confirmed virologic failure, at Week 144, or at time of early study drug discontinuation. The development of one or more primary FTC, TAF, or EVG resistance-associated mutations was observed in 12 of 22 patients with evaluable genotypic data from paired baseline and EVG+COBI+FTC+TAF treatment-failure isolates (12 of 866 patients [1.4%]) compared with 12 of 20 treatment-failure isolates from patients with evaluable genotypic data in the EVG+COBI+FTC+TDF group (12 of 867 patients [1.4%]). Of the 12 patients with resistance development in the EVG+COBI+FTC+TAF group, the mutations that emerged were M184V/I (N=11) and K65R/N (N=2) in reverse transcriptase and T66T/A/I/V (N=2), E92Q (N=4), Q148Q/R (N=1), and N155H (N=2) in integrase. Of the 12 patients with resistance development in the EVG+COBI+FTC+TDF group, the mutations that emerged were M184V/I (N=9), K65R/N (N=4), and L210W (N=1) in reverse transcriptase and E92Q/V (N=4), Q148R (N=2), and N155H/S (N=3) in integrase. In both treatment groups most patients who developed resistance mutations to EVG in integrase also developed resistance mutations to FTC in reverse transcriptase.

In phenotypic analyses of patients in the final resistance analysis population, 8 of 22 patients (36%) receiving EVG+COBI+FTC+TAF had HIV-1 isolates with reduced susceptibility to FTC compared with 7 of 20 patients (35%) receiving EVG+COBI+FTC+TDF. Finally, 7 of 22 patients (32%) had reduced susceptibility to EVG in the EVG+COBI+FTC+TAF group compared with 7 of 20 patients (35%) in the EVG+COBI+FTC+TDF group. One patient in the EVG+COBI+FTC+TAF group (1 of 22 [4.5%]) and 2 patient in the EVG+COBI+FTC+TDF group (2 of 20 [10%]) had reduced susceptibility to tenofovir.

Rilpivirine-Containing Regimens

In the cumulative Week 96 pooled resistance analysis for patients receiving RPV in combination with FTC+TDF in clinical studies TMC278-C209 and TMC278-C215 *(see Clinical Studies)* (N=550), resistance information was available for 71 of 78 patients who qualified for resistance analysis; 43 of these patients had an amino acid substitution associated with NNRTI (N=39) or NRTI (N=41) resistance. Among patients receiving efavirenz in combination with FTC+TDF, resistance information was available for 30 of 37 patients who qualified for resistance analysis; 17 of these patients had an amino acid substitution associated with NNRTI (N=15) or NRTI (N=8) resistance.

The NNRTI resistance substitutions that developed most commonly in patients receiving RPV were: V90I, K101E, E138K/Q, V179I, Y181C, V189I, H221Y, and F227C. The presence of the substitutions V90I and V189I at baseline did not affect the virologic response. The E138K substitution emerged most frequently during RPV treatment, commonly in combination with the M184I substitution. The amino acid substitutions associated with NRTI resistance that developed in 3 or more patients were: K65R, K70E, M184V/I, and K219E during the treatment period.

Through Week 96, fewer patients in the RPV arm with baseline viral load ≤100,000 copies/mL had emerging resistance-associated substitutions and/or phenotypic resistance to RPV (7/288) than patients with baseline viral load >100,000 copies/mL (30/262). Among those patients who developed resistance to RPV, 4/7 patients with baseline viral load ≤100,000 copies/mL and 28/30 patients with baseline viral load >100,000 copies/mL had cross-resistance to other NNRTIs.

In Virologically Suppressed Patients

Emtricitabine and Tenofovir Alafenamide

One subject with emergent resistance to FTC was identified (M184M/I) in a clinical study of virologically suppressed patients who switched from a regimen containing FTC+TDF to FTC+TAF given with EVG+COBI in a fixed-dose combination tablet (GS-US-292-0109, N=959).

ODEFSEY® Studies

Through Week 96, in patients who switched to ODEFSEY® from FTC/RPV/TDF or EFV/FTC/TDF (Studies GS-US-366-1216 and GS-US-366-1160; N=754, respectively), resistance information was available for 11 patients. No resistance-associated mutations were detected.

Cross Resistance

In HIV-1 Infected Treatment-Naïve Patients or Virologically Suppressed Patients

Considering all of the available *in vitro* and *in vivo* data in treatment-naïve patients the following resistance-associated substitutions, when present at baseline, may affect the activity of ODEFSEY®: K65R, K70E, K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, M184I, M184V, Y188L, H221Y, F227C, M230I M230L, and the combination of L100I+K103N.

Emtricitabine

FTC-resistant viruses with the M184V/I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine — thymidine analogue-associated mutations—TAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution or other substitutions associated with resistance to NNRTIs was susceptible to FTC.

Rilpivirine-Containing Regimen

No significant cross-resistance has been demonstrated between RPV-resistant HIV-1 variants to FTC or tenofovir, or between FTC- or tenofovir-resistant variants and RPV.

In Treatment-Naïve Adult Patients

In the Week 96 pooled analysis for patients receiving RPV in combination with FTC+TDF in clinical studies TMC278-C209 and TMC278-C215 *(*see *Clinical Studies)*, 66 patients with virologic failure had available phenotypic resistance data at virologic failure, 40 had reduced susceptibility to FTC, 31 had reduced susceptibility to RPV, and 2 had reduced susceptibility to tenofovir. Among these subjects, 39 had reduced susceptibility to lamivudine, 31 to etravirine, 28 to efavirenz, and 13 to nevirapine. Reduced susceptibility was observed to abacavir and/or didanosine in some cases.

Virologically Suppressed Adult Patients

In Study GS-US-264-0106, 4 of the 469 patients that switched from a protease inhibitor-based regimen to FTC/RPV/TDF had reduced susceptibility to at least one component of FTC/RPV/TDF through Week 48. Among these patients, all 4 had reduced susceptibility to FTC and 2 had reduced susceptibility to RPV. Patients with resistance to FTC also were resistant to lamivudine. These patients with resistance to RPV developed phenotypic cross-resistance to the other NNRTIs delavirdine, efavirenz, and nevirapine, but remained susceptible to etravirine in 1 of 2 cases.

In Vitro

In a panel of 67 HIV-1 recombinant laboratory strains with one amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, RPV showed antiviral activity against 64 (96%) of these strains. The single amino acid substitutions associated with a loss of susceptibility to RPV were: K101P and Y181V/I. The K103N substitution did not result in reduced susceptibility to RPV by itself, but the combination of K103N with L100I resulted in a 7-fold reduced susceptibility to RPV. In another study, the Y188L substitution resulted in a reduced susceptibility to RPV of 9-fold for clinical isolates and 6-fold for site-directed mutants.

Tenofovir Alafenamide

The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, FTC, and tenofovir, but retain sensitivity to zidovudine.

Multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R showed reduced susceptibility to TAF.

HIV-1 containing the K103N or Y181C mutations associated with resistance to NNRTIs was susceptible to TAF.

HIV-1 containing mutations associated with resistance to PIs, such as M46I, I54V, V82F/T, and L90M, were susceptible to TAF.

Effects on Electrocardiogram

Rilpivirine

The effect of RPV at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomized, placebo, and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady-state. RPV at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc.

When supratherapeutic doses of 75 mg once daily and 300 mg once daily of RPV were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) ms, respectively. Steady-state administration of RPV 75 mg once daily and 300 mg once daily

resulted in a mean C_{max} approximately 2.6-fold and 6.7-fold, respectively, higher than the mean steady-state C_{max} observed with the recommended 25 mg once daily dose of RPV.

Tenofovir Alafenamide

In a thorough QT/QTc study in 48 healthy subjects, TAF at the therapeutic dose or at a supratherapeutic dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

Clinical studies

Clinical efficacy of ODEFSEY® was established from studies conducted with FTC+TAF when given with cobicistat (COBI)-boosted elvitegravir (EVG) as a fixed-dose combination (EVG/COBI/FTC/TAF); from studies of RPV when given with FTC/TDF as individual components or as a fixed-dose combination FTC/RPV/TDF; and from studies of ODEFSEY®.

Emtricitabine+Tenofovir Alafenamide-Containing Regimens

Treatment-Naïve and Virologically Suppressed Patients

In both Study GS-US-292-0104 and Study GS-US-292-0111, patients were randomized in a 1:1 ratio to receive either FTC+TAF (N=866) once daily or FTC+TDF (N=867) once daily, both given with EVG+COBI as a fixed-dose combination tablet.

In Study GS-US-292-0104 and Study GS-US-292-0111, the mean age was 36 years (range, 18−76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL (range: 1.3−7.0). The mean baseline CD4+ cell count was 427 cells/mm^3 (range: 0−1360) and 13% had CD4+ cell counts less than 200 cells/mm^3. Twenty-three percent of patients had baseline viral loads greater than 100,000 copies/mL.

In both studies, patients were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies/mL, greater than 100,000 copies per mL to less than or equal to 400,000 copies/mL, or greater than 400,000 copies/mL), by CD4 count (less than 50 cells/μL, 50−199 cells/μL, or greater than or equal to 200 cells/μL), and by region (US or ex-US).

In Study GS-US-292-0109, the efficacy and safety of switching from either EFV/FTC/TDF, FTC/TDF plus atazanavir (boosted by either COBI or ritonavir), or EVG/COBI/FTC/TDF to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet were evaluated in a randomized, open-label study of virologically suppressed (HIV-1 RNA <50 copies/mL) HIV-1 infected adults (N=1436). Patients must have been stably suppressed (HIV-1 RNA <50 copies/mL) on their baseline regimen for at least 6 months and had no resistance mutations to FTC, TAF, or EVG prior to study entry. Patients were randomized in a 2:1 ratio to either switch to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet at baseline (N=959), or stay on their baseline antiretroviral regimen (N=477). Patients had a mean age of 41 years (range, 21−77), 89% were male, 67% were White, and 19% were Black. The mean baseline CD4+ cell count was 697 cells/mm^3 (range, 79−1951).

Patients were stratified by prior treatment regimen. At screening, 42% of patients were receiving FTC/TDF plus atazanavir (boosted by either COBI or ritonavir), 32% of patients were receiving EVG/COBI/FTC/TDF, and 26% of patients were receiving EFV/FTC/TDF.

Treatment outcomes of Studies GS-US-292-0104 and GS-US-292-0111 through 48 and 144 weeks; and GS-US-292-0109 through 48 weeks are presented in Table 2.

Table 2. Virologic Outcomes of Studies GS-US-292-0104 and GS-US-292-0111, and GS-US-292-0109

	Treatment-Naïve Adults in Studies GS-US-292-0104 and GS-US-292-0111				Virologically Suppressed Adults in Study GS-US-292-0109	
	Week 48[a]		Week 144[b]		Week 48[a]	
	FTC+TAF (Administered as EVG/COBI/FTC/ TAF) (N=866)	FTC+TDF (Administered as EVG/COBI/FTC/ TDF) (N=867)	FTC+TAF (Administered as EVG/COBI/FTC/ TAF) (N=866)	FTC+TDF (Administered as EVG/COBI/FTC/ TDF) (N=867)	FTC+TAF (Administered as EVG/COBI/FTC/ TAF) (N=959)	Baseline Regimen (N=477)
HIV-1 RNA <50 copies/mL	92%	90%	84%	80%	97%	93%
Treatment Difference	2.0% (95% CI=−0.7% to 4.7%)		4.2% (95% CI=0.6% to 7.8%)		4.1% (95% CI=1.6% to 6.7%)	
HIV-1 RNA ≥50 copies/mL[c]	4%	4%	5%	4%	1%	1%
No Virologic Data at Week 48 or 144 Window	4%	6%	11%	16%	2%	6%
Discontinued Study Drug Due to AE or Death[d]	1%	2%	1%	3%	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[e]	2%	4%	9%	11%	1%	4%
Missing Data During Window but on Study Drug	1%	<1%	1%	1%	0%	<1%

[a] Week 48 window was between Day 294 and 377 (inclusive).

[b] Week 144 window was between Day 966 and 1049 (inclusive).

[c] Included patients who had HIV-1 RNA ≥50 copies/mL in the Week 48 or Week 144 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.

[d] Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[e] Includes patients who discontinued for reasons other than an AE, death, or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

In Studies GS-US-292-0104 and GS-US-292-0111, at Week 144, FTC+TAF demonstrated statistical superiority (p=0.021) in achieving HIV-1 RNA <50 copies/mL when compared to FTC+TDF, both given with EVG+COBI as a fixed-dose combination tablet. The difference in perentage was 4.2% (95% CI: 0.6% to 7.8%). The rate of virologic success was similar across patient subgroups (age, gender, race, baseline HIV-1 RNA, or baseline CD4 count).

In Study GS-US-292-0109, switching to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet was superior in maintaining HIV-1 RNA <50 copies/mL when compared to patients who stayed on their baseline regimen. At Week 48, in patients who had received EFV/FTC/TDF as their prior treatment regimen, 96% (241/251) of those who switched to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet remained suppressed (HIV-1 RNA <50 copies/mL) vs. 90% (112/125) of those who stayed on EFV/FTC/TDF; in patients who had received FTC/TDF plus boosted atazanavir, 97% (390/402) of those who switched remained suppressed vs. 92% (183/199) of those who stayed on FTC/TDF plus boosted

atazanavir; in patients who had received EVG/COBI/FTC/TDF, 98% (301/306) of those who switched remained suppressed vs. 97% (149/153) of those who stayed on EVG/COBI/FTC/TDF.

In studies GS-US-292-0104 and GS-US-292-0111 in treatment-naïve patients, the mean increase from baseline in CD4+ cell count at Week 144 was 326 cells/mm^3 in patients receiving FTC+TAF and 305 cells/mm^3 in patients receiving FTC+TDF (p=0.06); and in Study GS-US-292-0109 in virologically suppressed patients, the mean increase from baseline in CD4+ cell count at Week 48 was 35 cells/mm^3 in patients who switched and 24 cells/mm^3 in those who stayed on their baseline regimen.

Bone Mineral Density

In a pooled analysis of treatment naïve patients in Studies GS-US-292-0104 and GS-US-292-0111, the effects of FTC+TAF compared to that of FTC+TDF on bone mineral density (BMD) change from baseline to Week 144 were assessed by dual-energy x-ray absorptiometry (DXA). As shown in Table 3, in patients who had both baseline and Week 144 measurements (N=690 and 702 in the FTC+TAF group and N=683 and 686 in the FTC+TDF group, for hip and spine, respectively), there were smaller decreases in BMD in treatment-naïve patients receiving FTC+TAF as compared with patients receiving FTC+TDF, both given with EVG+COBI as a fixed-dose combination tablet. In virologically suppressed patients, changes in BMD were assessed by DXA in those who had both baseline and Week 48 measurements (N=869 and 881 in the FTC+TAF given with EVG+COBI group and N=428 and 436 in the group of patients who remained on their baseline FTC+TDF+third agent regimen, for hip and spine, respectively). There were increases from baseline in mean BMD at the hip and at the spine in the EVG/COBI/FTC/TAF group as compared with minimal changes from baseline in both parameters in the FTC+TDF+third agent group.

Table 3. Measures of Bone Mineral Density (Week 48 and 144 Analysis)

	Treatment-Naïve Adults in Studies GS-US-292-0104 and GS-US-292-0111 (Week 144)			**Virologically Suppressed Adults in Study GS-US-292-0109 (Week 48)**		
	FTC+TAF (Administered as EVG/COBI/FTC/TAF)	**FTC+TDF (Administered as EVG/COBI/FTC/TDF)**	**Treatment Difference**	**FTC+TAF (Administered as EVG/COBI/FTC/TAF)**	**Baseline Regimen**	**Treatment Difference**
Hip DXA Analysis	**N=690**	**N=683**		**N=869**	**N=428**	
Mean Percent Change in BMD	−0.8%	−3.4%	2.62% p<0.001	1.5%	−0.3%	1.81% p<0.001
Patients with Categorical Change:			--			--
>3% Decrease in BMD	28%	55%		3%	13%	
>3% Increase in BMD	13%	6%		21%	8%	
Patients with No Decrease (≥zero % change) in BMD	40%	19%	--	78%	46%	--
Lumbar Spine DXA Analysis	**N=702**	**N=686**		**N=881**	**N=436**	
Mean Percent Change in BMD	−0.9%	−3.0%	2.04% p<0.001	1.6%	−0.4%	2% p<0.001
Patients with			--			--

Categorical Change: >3% Decrease in BMD >3% Increase in BMD	30% 13%	49% 7%		8% 33%	19% 13%	
Patients with No Decrease (≥zero % change) in BMD	39%	22%	--	74%	47%	--

Renal Laboratory Parameters

In the pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111 in treatment-naïve adult patients, statistically significant differences were observed between treatment groups that favored TAF for increases in serum creatinine and changes in proteinuria, including Urine Protein to Creatinine Ratio (UPCR), Urine Albumin to Creatinine Ratio (UACR), urine retinol binding protein (RBP) to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio. The mean ±SD change in serum creatinine after 144 weeks of treatment was 0.04±0.12 mg/dL for the FTC+TAF group and 0.07±0.13 mg/dL for the FTC+TDF group ($p<0.001$ for treatment difference). Treatment emergent proteinuria was observed in 40% of subjects receiving FTC+TAF and in 45% of subjects receiving FTC+TDF ($p=0.027$ for treatment difference).

In virologically suppressed patients in Study GS-US-292-0109, there were decreases from baseline in proteinuria (UPCR), albuminuria (UACR), and tubular proteinuria (urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio), and other measures of proximal renal tubular dysfunction (including fractional excretion of uric acid [FEUA]) in patients receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet, as compared with increases from baseline in patients who stayed on their FTC+TDF-containing baseline regimen, collectively indicating the reduced impact of TAF on proximal renal tubular function. At Week 48, the median percentage change in UPCR was −21% vs. 10%; in UACR it was −18% vs. 9%. At Week 48, the median percentage change in urine RBP to creatinine ratio was −33% vs. 18%; and in urine beta-2-microglobulin to creatinine ratio it was −52% vs. 19% ($p <0.001$ for all comparisons).

Changes in Lipid Laboratory Tests

Increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct LDL, HDL, and triglycerides at Week 144. The median increase from baseline for these parameters was greater in patients receiving FTC+TAF compared with patients receiving FTC+TDF, both given with EVG+COBI as a fixed-dose combination tablet ($p<0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL, HDL, and triglycerides). Median (Q1, Q3) change from baseline at Week 144 in total cholesterol to HDL ratio was 0.2 (–0.3, 0.7) in patients receiving FTC+TAF and 0.1 (–0.4, 0.6) in patients receiving FTC+TDF ($p=0.006$ for the difference between treatment groups). Mean changes from baseline in lipid values are provided in Table 4.

Table 4. Lipid Values, Mean Change from Baseline in Studies GS-US-292-0104 and GS-US-292-0111				
	FTC+TAF (Administered as EVG/COBI/FTC/TAF) N=799		FTC+TDF (Administered as EVG/COBI/FTC/TDF) N=797	
	Baseline	Week 144	Baseline	Week 144
	mg/dL	Change[a,b]	mg/dL	Change[a,b]
Total Cholesterol (fasted)	162 [N=647]	+31 [N=647]	165 [N=627]	+14 [N=627]
HDL-Cholesterol (fasted)	47 [N=647]	+7 [N=647]	46 [N=627]	+3 [N=627]
LDL-Cholesterol (fasted)	103 [N=643]	+20 [N=643]	107 [N=628]	+8 [N=628]
Triglycerides (fasted)	111 [N=647]	+29 [N=647]	115 [N=627]	+17 [N=627]
Total Cholesterol to HDL ratio	3.7 [N=647]	0.2 [N=647]	3.8 [N=627]	0.1 [N=627]

[a] The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week-144 values.

[b] Subjects who received lipid-lowering agents during the treatment period were excluded.

HIV-1 Infected Patients with Renal Impairment

In Study GS-US-292-0112, the efficacy and safety of FTC+TAF were evaluated in an open-label clinical study, in which 242 HIV-1 infected patients with mild to moderate renal impairment (eGFR by Cockcroft-Gault method between 30 to 69 mL/minute) switched to FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. Patients were virologically suppressed (HIV-1 RNA <50 copies/mL) for at least 6 months before switching.

The mean age was 58 years (range, 24−82), with 63 patients (26%) who were ≥65 years of age. Seventy-nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirteen percent of patients identified as Hispanic/Latino. Thirty-five percent of patients were on a treatment regimen that did not contain TDF. At baseline, median eGFR was 56 mL/minute, and 33% of patients had an eGFR from 30 to 49 mL/minute. The mean baseline CD4+ cell count was 664 cells/mm^3 (range, 126−1813).

At Week 24, 95% (230/242 patients) maintained HIV-1 RNA <50 copies/mL after switching to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet. At Week 144, 83.1% (197/237) maintained HIV-1 RNA <50 copies after switching to FTC+TAF given with EVG+COBI.

In a substudy (N=32), patients had no change from baseline in their actual glomerular filtration rate at Week 24, as measured by iohexol clearance.

Changes from baseline in renal laboratory tests in Study GS-US-292-0112 are summarized in Table 5.

Table 5. Change from Baseline in Renal Laboratory Tests at Week 144 in Virologically Suppressed Patients with Renal Impairment who Switched to FTC+TAF (Administered as EVG/COBI/FTC/TAF) in Study GS-US-292-0112 (Week 144 Analysis)	
	FTC+TAF (Administered as EVG/COBI/FTC/TAF) N=242
Serum Creatinine (mg/dL)[a]	−0.05±0.29

Improvement in Proteinuria by Urine Dipstick[b]	56/66 (85%)
Urine Protein to Creatinine Ratio [UPCR][c]	−45.7%
Urine Albumin to Creatinine Ratio [UACR][c]	−35.1%
Urine RBP to Creatinine Ratio[c]	−63.8%
Urine Beta-2-Microglobulin to Creatinine Ratio[c]	−81.9%

[a] Mean change ± SD
[b] An improvement of at least 1 toxicity grade from baseline
[c] Median percent change

Multiple assessments of renal function indicate that improvements in renal function occur as early as 1 week after the switch to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet and persist through 144 weeks. The prevalence of clinically significant proteinuria (UPCR >200 mg/g) and albuminuria (UACR ≥30 mg/g) decreased from 42% at baseline to 16% at Week 144 and 49% at baseline to 32% at Week 144, respectively. Other renal assessments, including fractional excretion of uric acid, serum cystatin C, and serum phosphorus showed small changes from baseline through Week 144.

In patients whose prior antiretroviral regimen did not include TDF (N=84), mean change from baseline in serum creatinine at week 144 was 0.01±0.31 mg/dL; 73% (11/15 patients) had an improvement in proteinuria as measured by urine dipstick. Median percent change in UPCR and UACR at Week 144 were −9% and -4%, respectively. Median percent change in urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio at Week 144 were 15% and 6%, respectively.

In virologically suppressed patients with renal impairment who switched to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet, mean percentage increases from baseline at Week 144 were observed in hip and spine BMD. Assessment of BMD using a threshold of 3% for changes from baseline revealed higher percentages of patients had increases versus decreases from baseline in BMD at both hip and spine.

In 84 renally impaired patients who switched to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet in Study GS-US-292-0112 from antiviral regimens not containing TDF, mean change from baseline in fasting lipid laboratory tests at Week 144 were −19 mg/dL in total cholesterol, −13 mg/dL in LDL-cholesterol, −6 mg/dL in HDL-cholesterol, 0.2 in total cholesterol to HDL ratio, and 22 mg/dL in triglycerides.

Pediatric Patients

In Study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of FTC+TAF were evaluated in an open-label study, in which HIV-1-infected treatment-naïve adolescents (N=50), received FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. Patients had a mean age of 15 years (range, 12 to 17), 44% were male, 12% were Asian, and 88% were Black. At baseline, mean plasma HIV-1 RNA was 4.6 log10 copies/mL, median CD4+ cell count was 456 cells/mm^3 (range, 95 to 1110), and median CD4+% was 23% (range, 7% to 45%). 22% had baseline plasma HIV-1 RNA >100,000 copies/mL.

At Week 48, 92% (46/50) achieved HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm^3. Three of 50 patients had virologic

failure by snapshot at Week 48; no emergent resistance to FTC+TAF was detected though Week 48.

Among the treatment-naïve adolescent patients who had both baseline and Week 48 measurements (N=47 and 44 for the lumbar spine and total body less head [TBLH], respectively), mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for TBLH.

Rilpivirine-Containing Regimens

Treatment-Naïve Patients

Studies TMC278-C209 and TMC278-C215

The efficacy of RPV versus efavirenz in combination with FTC/TDF was evaluated in two randomized, double-blind, double-dummy, controlled studies (Study TMC278-C209 and FTC/TDF subset of Study TMC278-C215) in treatment-naïve, HIV-1 infected patients (N=1368). The studies are identical in design with the exception of the background regimen (BR). Patients were randomized in a 1:1 ratio to receive either RPV 25 mg (N=686) once daily or efavirenz 600 mg (N=682) once daily in addition to a BR. In TMC278-C209 (N=690), the BR was FTC/TDF. In TMC278-C215 (N=678), the BR consisted of 2 nucleoside reverse transcriptase inhibitors (NRTIs): FTC/TDF (60%, N=406) or lamivudine/zidovudine (30%, N=204) or abacavir plus lamivudine (10%, N=68).

For patients who received FTC+TDF (N=1096) in TMC278-C209 and TMC278-C215, the mean age was 37 years (range, 18–78), 78% were male, 62% were White, 24% were Black, and 11% were Asian. The mean baseline CD4+ cell count was 265 cells/mm^3 (range, 1–888) and median baseline plasma HIV-1 RNA was 5 $\log_{10}$ copies/mL (range, 2–7). Patients were stratified by baseline HIV-1 RNA. Fifty percent of patients had baseline viral loads >100,000 copies/mL and 31% had CD4+ cell counts <200 cells/mm^3.

Treatment outcomes through 96 weeks are presented in Table 6. At Week 48 and Week 96, RPV administered in combination with FTC/TDF was noninferior in achieving HIV-1 RNA <50 copies/mL when compared to efavirenz administered in combination with FTC/TDF. The virologic failure rate in the RPV arm at Week 48 and at Week 96 was 9% and 11%, respectively, and 4% and 5% in the efavirenz arm. The difference in the rate of new virologic failures from Week 48 to Week 96 between RPV and efavirenz arms was not statistically significant (3.6% and 2.1%, respectively, p=0.242). Discontinuations due to adverse events were higher in the efavirenz arm at Week 96 than the RPV arm.

Table 6. Virologic Outcomes of Randomized Treatment of Studies TMC278-C209 and TMC278-C215 in Adults (Pooled Data for Patients Receiving Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir disoproxil fumarate) at Week 48 and Week 96

	Outcome at Week 48		**Outcome at Week 96**	
	Rilpivirine + FTC/TDF	**Efavirenz + FTC/TDF**	**Rilpivirine + FTC/TDF**	**Efavirenz + FTC/TDF**
	N=550	**N=546**	**N=550**	**N=546**
HIV-1 RNA <50 copies/mL[a] (TLOVR[b])	83% (459/550)	82% (450/546)	77% (423/550)	77% (422/546)
% Difference (95% CI)[c]	1% (-3% to 6%)	0% (-5% to 5%)		

By baseline viral load (copies/mL)				
≤100000	90% (258/288)	85% (217/256)	84% (241/288)	81% (206/255)
>100000	77% (201/262)	80% (233/290)	69% (182/262)	74% (216/291)
>100000 to ≤500000	79% (166/209)	82% (180/219)	71% (149/209)	75% (164/219)
>500000	66% (35/53)	75% (53/71)	62% (33/53)	72% (52/72)
By $CD4^+$ count ($cells/mm^3$)				
<200	76% (138/181)	80% (132/164)	67% (122/181)	73% (119/164)
≥200	87% (321/368)	83% (318/382)	82% (301/368)	79% (303/382)
Virologic Failure[d]	9% (52/550)	4% (23/546)	11% (63/550)	5% (28/546)
By baseline viral load (copies/mL)				
≤100000	4% (12/288)	2% (6/256)	6% (17/288)	2% (6/255)
>100000	15% (40/262)	6% (17/290)	18% (46/262)	8% (22/291)
>100000 to ≤500000	13% (27/209)	4% (9/219)	16% (34/209)	6% (13/219)
>500000	25% (13/53)	11% (8/71)	23% (12/53)	13% (9/72)
By $CD4^+$ count ($cells/mm^3$)				
<200	15% (28/181)	7% (12/164)	20% (36/181)	9% (14/164)
≥200	7% (24/368)	3% (11/382)	7% (27/368)	4% (14/382)
Death	0	0.2% (1/546)	0	1% (4/546)
Discontinued due to adverse event (AE)	2% (12/550)	7% (39/546)	4% (20/550)	8% (44/546)
Discontinued for non-AE reason[e]	5% (27/550)	6% (33/546)	8% (44/550)	9% (48/546)

[a] Patients achieved virologic response (two consecutive viral loads <50 copies/mL) and maintained it through week 48 or 96.

[b] TLOVR=Time to loss of virologic response.

[c] Ninety-five percent confidence interval was computed using normal approximation.

[d] Includes patients who were rebounder (confirmed viral load ≥50 copies/mL after being responder) or who were never suppressed (no confirmed viral load <50 copies/mL, either ongoing or discontinued due to lack or loss of efficacy).

[e] e.g. lost to follow-up, non-compliance, withdrew consent.

At Week 96, the mean change from baseline in CD4+ cell count was +226 $cells/mm^3$ in the RPV/FTC/TDF arm and +222 $cells/mm^3$ in the efavirenz arm in the pooled analysis of the ECHO and THRIVE studies (estimated treatment difference [95% CI]: +8 [−13 to 28]).

Virologic outcomes were comparable in males and females in Studies TMC278-C209 and TMC278-C215.

Changes in Lipid Laboratory Tests

In Studies C209 and C215, changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in Table 7. The clinical benefit of these findings has not been demonstrated.

Table 7. Pooled Lipid Values Reported in Subjects Receiving RPV or Efavirenz in Combination with FTC/TDF in Studies C209 and C215[a] (Week 96)

Mean	**Rilpivirine + FTC/TDF N=550**		**Efavirenz + FTC/TDF N=546**	
	Baseline	**Week 96**	**Baseline**	**Week 96**
	Mean (mg/dL)	**Mean Change[b] (mg/dL)**	**Mean (mg/dL)**	**Mean Change[b] (mg/dL)**
Total Cholesterol (fasted)	162 [N=430]	2 [N=430]	160 [N=401]	26 [N=401]
HDL-Cholesterol	42 [N=429]	4 [N=429]	40 [N=399]	11 [N=399]

Table 7. Pooled Lipid Values Reported in Subjects Receiving RPV or Efavirenz in Combination with FTC/TDF in Studies C209 and C215[a] (Week 96)				
(fasted)				
LDL-Cholesterol (fasted)	97 [N=427]	−1 [N=427]	96 [N=397]	14 [N=397]
Triglycerides (fasted)	123 [N=430]	−14 [N=430]	127 [N=401]	6 [N=401]

[a] Excludes subjects who received lipid-lowering agents during the treatment period.

[b] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week-96 values.

Pediatric Patients

Study TMC278-C213

The pharmacokinetics, safety, tolerability, and efficacy of RPV 25 mg once daily, in combination with an investigator-selected BR containing two NRTIs, was evaluated in Study TMC278-C213, a single-arm, open-label Phase 2 study in antiretroviral treatment-naïve HIV-1 infected pediatric patients 12 to less than 18 years of age and weighing at least 32 kg. This analysis included 36 patients who had completed at least 48 weeks of treatment or discontinued earlier. The median duration of exposure for patients was 63.5 weeks.

The 36 patients had a median age of 14.5 years (range, 12−17 years) and were 55.6% female, 88.9% Black, and 11.1% Asian. The median baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL, and the median baseline CD4+ cell count was 414 x 10^6 cells/L (range, 25−983 × 10^6 cells/L). The proportion of patients with HIV-1 RNA <50 copies/mL at Week 48 (TLOVR) was 72.2% (26/36). The combination of NRTIs most frequently used together with RPV was FTC/TDF (24 subjects [66.7%]), followed by 3TC/TDF (8 subjects [22.2%]) and 3TC/AZT (4 subjects [11.1%]).

The proportion of responders was higher in subjects with a baseline viral load ≤100,000 copies/mL (78.6%, 22/28) as compared to those with a baseline viral load >100,000 copies/mL (50.0%, 4/8). The proportion of virologic failures was 22.2% (8/36). The proportion of virologic failures was lower in subjects with a baseline viral load ≤100,000 copies/mL (17.9%, 5/28) as compared to those with a baseline viral load >100,000 copies/mL (37.5%, 3/8). One subject discontinued due to an adverse event and 1 subject discontinued due to reasons other than an adverse event or virologic failure. At Week 48, the mean increase in CD4+ cell count from baseline was 201.2 × 10^6 cells/L.

ODEFSEY®

Virologically Suppressed Patients

In Study GS-US-366-1216, the efficacy and safety of switching from FTC/RPV/TDF to ODEFSEY® were evaluated in a randomized, double-blind study of virologically suppressed HIV-1 infected adults. Patients must have been stably suppressed (HIV-1 RNA <50 copies/mL) on their baseline regimen of FTC/RPV/TDF for at least 6 months and had no known resistance mutations to FTC, TAF, or RPV prior to study entry. Patients were randomized in a 1:1 ratio to either switch to ODEFSEY® (N=316) or stay on FTC/RPV/TDF (N=314). Patients had a mean

age of 45 years (range: 23−72), 90% were male, 75% were White, and 19% were Black. The mean baseline CD4+ cell count was 709 cells/mm^3 (range: 104−2527).

In Study GS-US-366-1160, the efficacy and safety of switching from EFV/FTC/TDF to ODEFSEY® were evaluated in a randomized, double-blind study of virologically suppressed HIV-1 infected adults. Patients must have been stably suppressed (HIV-1 RNA <50 copies/mL) on their baseline regimen of EFV/FTC/TDF for at least 6 months and had no known resistance mutations to FTC, TAF, or RPV prior to study entry. Patients were randomized in a 1:1 ratio to either switch to ODEFSEY® (N=438) or stay on EFV/FTC/TDF (N=437). Patients had a mean age of 48 years (range: 19−76), 87% were male, 67% were White, and 27% were Black. The mean baseline CD4+ cell count was 700 cells/mm^3 (range: 140−1862).

Treatment outcomes of Studies GS-US-366-1216 and GS-US-366-1160 are presented in Table 8.

Table 8. Virologic Outcomes of Studies GS-US-366-1216 and GS-US-366-1160 at Weeks 48[a] and 96[b]

	GS-US-366-1216				GS-US-366-1160			
	Week 48		Week 96		Week 48		Week 96	
	ODEFSEY® (N=316)	FTC/RPV/ TDF (N=313)[c]	ODEFSEY® (N=316)	FTC/RPV/ TDF (N=313)[c]	ODEFSEY® (N=438)	EFV/FTC/ TDF (N=437)	ODEFSEY® (N=438)	EFV/FTC/ TDF (N=437)
HIV-1 RNA <50 copies/mL	94%	94%	89%	88%	90%	92%	85%	85%
Treatment Difference	-0.3% (95% CI = −4.2% to 3.7%)		0.7% (95% CI = −4.3% to 5.8%)		-2.0% (95% CI = −5.9% to 1.8%)		0% (95% CI = −4.8% to 4.8%)	
HIV-1 RNA ≥50 copies/mL[d]	1%	0%	1%	1%	1%	1%	1%	1%
No Virologic Data at Week 48 or 96 Window	6%	6%	10%	11%	9%	7%	14%	14%
Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA <50 copies/mL	2%	1%	2%	3%	3%	1%	4%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[e]	4%	4%	8%	8%	5%	5%	10%	11%
Missing Data During Window but on Study Drug	<1%	1%	1%	0	1%	1%	<1%	0

a Week 48 window was between Day 295 and 378 (inclusive).
b Week 96 window was between Day 631 and 714 (inclusive).
c One patient who was not on FTC/RPV/TDF prior to screening was excluded from the analysis.
d Included patients who had ≥50 copies/mL in the Week 48 or Week 96 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.
e Include patients who discontinued for reasons other than an AE, death, or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

At Week 96, switching to ODEFSEY® was noninferior in maintaining HIV-1 RNA <50 copies/mL when compared to patients who stayed on FTC/RPV/TDF or on EFV/FTC/TDF in respective studies.

In Study GS-US-366-1216, the mean change from baseline in CD4+ cell count at Week 96 was 12 cells/mm^3 in patients who switched to ODEFSEY® and -16 cells/mm^3 in those who remained on FTC/RPV/TDF. In Study GS-US-366-1160, the mean change from baseline in CD4+ cell count at Week 96 was 12 cells/mm^3 in patients who switched to ODEFSEY® and 6 cells/mm^3 in those who stayed on EFV/FTC/TDF.

Bone Mineral Density

In Studies GS-US-366-1216 and GS-US-366-1160, changes in BMD were assessed by DXA in patients who had both baseline and Week 96 measurements (Study GS-US-366-1216: N=160 and 162 in the ODEFSEY® arm, and N=156 and 158 in the FTC/RPV/TDF arm, for hip and spine, respectively; Study GS-US-366-1160: N=322 and 327 in the ODEFSEY® arm, and N=345 and 344 in the EFV/FTC/TDF arm, for hip and spine, respectively). In both studies, there were increases from baseline in mean BMD at the hip and at the spine in the ODEFSEY® groups as compared with minimal changes from baseline in both parameters in the FTC/RPV/TDF and EFV/FTC/TDF groups. Results are summarized in Table 9.

Table 9. Measures of Bone Mineral Density in Studies GS-US-366-1216 and GS-US-366-1160 (Week 96 Analysis)

	GS-US-366-1216			GS-US-366-1160		
	ODEFSEY®	**FTC/RPV/TDF**	**Treatment Difference**	**ODEFSEY®**	**EFV/FTC/TDF**	**Treatment Difference**
Hip DXA Analysis	**n=160**	**n=156**		**n=322**	**n=345**	
Mean Percent Change in BMD	1.6%	-0.6%	2.24% p<0.001	1.8%	-0.6%	2.45% p<0.001
Patients with Categorical Change:						
≥3% Decrease in BMD ≥3% Increase in BMD	5% 26%	13% 7%	--	5% 33%	18% 10%	--
Patients with No Decrease (≥ zero % change) in BMD	78%	43%	--	75%	40%	--
Lumbar Spine DXA Analysis	**n=162**	**n=158**		**n=327**	**n=344**	
Mean Percent Change in BMD	2.0%	-0.3%	2.29% p<0.001	1.7%	0.1%	1.58% p<0.001
Patients with Categorical Change:						
≥3% Decrease in BMD ≥3% Increase in BMD	4% 35%	24% 18%	--	9% 33%	17% 19%	--
Patients with No Decrease (≥ zero % change) in BMD	73%	46%	--	71%	52%	--

Renal Laboratory Parameters

In Study GS-US-366-1216, there were minimal changes or decreases from baseline in albuminuria (UACR), and tubular proteinuria (urine RBP to creatinine ratio, urine beta-2-microglobulin to creatinine ratio) in patients receiving ODEFSEY® as compared with increases from baseline in patients who stayed on FTC/RPV/TDF. At Week 96, the median percentage change in UACR was -9% vs. 33%; in urine RBP to creatinine ratio, it was -7% vs. 56%; and in urine beta 2-microglobulin to creatinine ratio, it was −16% vs. 44% for the ODEFSEY® and FTC/RPV/TDF groups, respectively (p<0.001 for the differences between treatment groups).

In Study GS-US-366-1160 there were decreases from baseline in albuminuria (UACR), and tubular proteinuria (urine RBP to creatinine ratio, urine beta-2-microglobulin to creatinine ratio)

in patients receiving ODEFSEY® as compared with increases from baseline in patients who stayed on EFV/FTC/TDF. At Week 96, the median percentage change in UACR was -1% vs. 40%; in urine RBP to creatinine ratio, it was -7.0% vs. 87%; and in urine beta 2-microglobulin to creatinine ratio, it was -32 vs. 68% for the ODEFSEY® and EFV/FTC/TDF groups, respectively ($p<0.001$ for the differences between treatment groups).

Changes in Lipid Laboratory Tests

Changes from baseline to Week 96 in the fasting lipid parameters total cholesterol, direct LDL, HDL, and triglycerides for Studies GS-US-366-1216 and GS-US-366-1160 are presented in Table 10. These changes were not considered clinically relevant.

Table 10. Lipid Values, Mean Change from Baseline in Studies GS-US-366-1216 and GS-US-366-1160

	GS-US-366-1216				GS-US-366-1160			
	ODEFSEY® N=316 [n=216]		FTC/RPV/TDF N=314 [n=228]		ODEFSEY® N=438 [n=225]		EFV/FTC/TDF N=437 [n=228]	
	Baseline	Week 96	Baseline	Week 96	Baseline	Week 96	Baseline	Week 96
	mg/dL	Change[a,b]	mg/dL	Change[a,b]	mg/dL	Change[a,b]	mg/dL	Change[a,b]
Total Cholesterol (fasted)	174	+21	170	+2	191	-6	190	-1
HDL-Cholesterol (fasted)	50	+3	48	+1	57	-5	56	0
LDL-Cholesterol (fasted)	110[c]	+17[c]	107[d]	+3[d]	116[e]	+2[e]	117	+2
Triglycerides (fasted)	114	+24	115	4	134	+1	131	+6
Total Cholesterol to HDL Ratio	3.7	+0.2	3.8	0	3.6	+0.2	3.7	+0.1

a The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 96 values.
b Subjects who received lipid-lowering agents during the treatment period were excluded.
c [n=217] for ODEFSEY® group in Study GS-US-366-1216 for LDL-Cholesterol (fasted)
d [n=227] for FTC/RPV/TDF group in Study GS-US-366-1216 for LDL-Cholesterol (fasted)
e [n=266] for ODEFSEY® group in Study GS-US-366-1160 for LDL-Cholesterol (fasted)

Pharmacokinetic Properties

Bioequivalence

FTC and TAF exposures were bioequivalent when comparing ODEFSEY® 200/25/25 mg to EVG/COBI/FTC/TAF (150/150/200/10 mg) fixed-dose combination tablet following single-dose administration to healthy subjects (N=82) under fed conditions.

RPV exposures were bioequivalent when comparing ODEFSEY® 200/25/25 mg to RPV 25 mg following single-dose administration to healthy subjects (N=95) under fed conditions.

Absorption

Emtricitabine

FTC is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours postdose. Following multiple dose oral administration of FTC to 20 HIV-1 infected subjects, the (mean±SD) area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0±3.1 hr•μg/mL. The mean steady-state plasma trough concentration at 24 hours postdose was equal to or greater than the mean *in vitro* IC90 value for anti-HIV-1 activity.

FTC systemic exposure was unaffected when FTC was administered with food.

Rilpivirine

The pharmacokinetic properties of RPV have been evaluated in adult healthy subjects, adult antiretroviral treatment-naïve HIV-1 infected patients, and antiretroviral treatment-naïve HIV-1 infected pediatric patients 12 years of age and older and weighing at least 32 kg. Exposure to RPV was generally lower in HIV-1 infected patients than in healthy subjects.

After oral administration, the maximum plasma concentration of RPV is generally achieved within 4 to 5 hours. The absolute bioavailability of RPV hydrochloride is unknown.

Relative to fasting conditions, the administration of ODEFSEY® to healthy adult subjects with food resulted in increased RPV exposure (AUC) by 13−73%.

Tenofovir Alafenamide

TAF is rapidly absorbed following oral administration, with peak plasma concentrations occurring at 15−45 minutes postdose.

Relative to fasting conditions, the administration of ODEFSEY® to healthy adult subjects with food resulted in increased TAF exposure (AUC) by 45−54%. These changes are not considered clinically meaningful.

It is recommended that ODEFSEY® be taken with food.

Distribution

Emtricitabine

In vitro binding of FTC to human plasma proteins was <4% and independent of concentration over the range of 0.02 to 200 μg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

Rilpivirine

RPV is approximately 99.7% bound to plasma proteins *in vitro*, primarily to albumin. The distribution of RPV into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Tenofovir Alafenamide

In vitro binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01–25 micrograms per mL. *Ex-vivo* binding of TAF to human plasma proteins in samples collected during clinical studies was approximately 80%.

Metabolism

Emtricitabine

In vitro studies indicate that FTC is not an inhibitor of human CYP450 enzymes. Following administration of ^{14}C-FTC, complete recovery of the FTC dose was achieved in urine (~86%) and feces (~14%). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of FTC includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable.

Rilpivirine

In vitro experiments indicate that RPV primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system.

Tenofovir Alafenamide

Metabolism is a major elimination pathway for TAF in humans, accounting for >80% of an oral dose. *In vitro* studies have shown that TAF is metabolized to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of TAF resulted in tenofovir diphosphate concentrations >4-fold higher in PBMCs and >90% lower concentrations of tenofovir in plasma as compared to a 300 mg oral dose of TDF.

In vitro, TAF is not metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. TAF is minimally metabolized by CYP3A4. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was not significantly affected. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

Elimination

Emtricitabine

The plasma FTC half-life was approximately 10 hours. Following FTC dosing, the steady-state mean intracellular half-life of FTC 5'-triphosphate (the active drug moiety) in PBMCs was 39 hours.

FTC is primarily excreted by the kidney by both glomerular filtration and active tubular secretion.

Rilpivirine

The terminal elimination half-life of RPV is approximately 45 hours. After single dose oral administration of ^{14}C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in feces and urine, respectively. In feces, unchanged RPV accounted for on average 25% of the administered dose. Only trace amounts of unchanged RPV (<1% of dose) were detected in urine.

Tenofovir Alafenamide

TAF is eliminated following metabolism to tenofovir. TAF and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Tenofovir is renally eliminated by both glomerular filtration and active tubular secretion. Renal excretion of intact TAF is a minor pathway with less than 1% of the dose eliminated in urine. The pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150−180 hours within PBMCs.

Linearity/Non-linearity

Emtricitabine

The multiple dose pharmacokinetics of FTC are dose proportional over the dose range of 25 mg to 200 mg.

Tenofovir Alafenamide

TAF exposures are dose proportional over the dose range of 8 mg to 125 mg.

Special populations

Age, Gender, and Ethnicity

No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for FTC, RPV, or TAF.

Rilpivirine

The pharmacokinetics of RPV in antiretroviral treatment-naïve HIV-1 infected pediatric patients 12 to less than 18 years of age receiving RPV 25 mg once daily was comparable to that in treatment-naïve HIV-1 infected adults receiving RPV 25 mg once daily. There was no impact of body weight on RPV pharmacokinetics in pediatric patients in study C213 (33 to 93 kg), similar to what was observed in adults. The pharmacokinetics of RPV in pediatric patients less than 12 years of age is under investigation. Population pharmacokinetic analysis in HIV-1 infected patients showed that RPV pharmacokinetics is not different across the age range (12 to 78 years) evaluated.

Emtricitabine and Tenofovir Alafenamide

Population pharmacokinetics analysis of HIV-infected patients in Phase 2 and Phase 3 studies of FTC+TAF given with EVG+COBI as a fixed-dose combination tablet showed that within the age range studied (12 to 82 years), age did not have a clinically relevant effect on exposures of TAF.

Exposures of FTC and TAF achieved in 24 pediatric patients aged 12 to <18 years were similar to exposures achieved in treatment-naïve adults.

Renal impairment

Emtricitabine

FTC is principally eliminated by renal excretion, and the exposure to FTC increases in patients with renal impairment.

Rilpivirine

The pharmacokinetics of RPV have not been studied in patients with renal insufficiency. Renal elimination of RPV is negligible. Therefore, the impact of renal impairment on RPV elimination is expected to be minimal. As RPV is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

Tenofovir Alafenamide

No clinically relevant differences in TAF or tenofovir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment (estimated creatinine clearance less than 30 mL/minute) in studies of TAF. There are no pharmacokinetic data on TAF in patients with creatinine clearance less than 15 mL/minute.

Hepatic impairment

Emtricitabine

The pharmacokinetics of FTC have not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Rilpivirine

RPV is primarily metabolized and eliminated by the liver. In a study in adults comparing 8 patients with mild hepatic impairment (Child Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child Pugh score B) to 8 matched controls, the multiple dose exposure of RPV was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. No RPV dose adjustment is required in patients with mild or moderate hepatic impairment. RPV has not been studied in patients with severe hepatic impairment (Child Pugh score C).

Tenofovir Alafenamide

Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild, moderate, or severe hepatic impairment, and no TAF dose adjustment is required in patients with hepatic impairment.

Hepatitis B and/or Hepatitis C Virus Coinfection

Pharmacokinetics of FTC, RPV, and TAF have not been fully evaluated in patients coinfected with hepatitis B and/or C virus.

Pregnancy and Postpartum

The exposure to total rilpivirine after intake of rilpivirine 25 mg once daily as part of an antiretroviral regimen was lower during pregnancy (similar for the 2nd and 3rd trimester) compared with postpartum (see Table 11). The decrease in unbound (i.e., active) rilpivirine pharmacokinetic parameters during pregnancy compared to postpartum was less pronounced than for total rilpivirine.

In women receiving rilpivirine 25 mg once daily during the 2nd trimester of pregnancy, mean intra-individual values for total rilpivirine C_{max}, AUC_{24h} and C_{min} values were, respectively, 21%, 29% and 35% lower as compared to postpartum; during the 3rd trimester of pregnancy, C_{max}, AUC_{24h} and C_{min} values were, respectively, 20%, 31% and 42% lower as compared to postpartum.

Table 11: Pharmacokinetic Results of Total Rilpivirine After Administration of Rilpivirine 25 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total rilpivirine[a] (mean±SD, t_{max}: median [range])	**Postpartum (6-12 Weeks) (n=11)**	**2nd Trimester of pregnancy (n=15)**	**3rd Trimester of pregnancy (n=13)**
C_{min}, ng/mL	84.0 ± 58.8	54.3 ± 25.8	52.9 ± 24.4
C_{max}, ng/mL	167 ± 101	121 ±45.9	123 ± 47.5
t_{max}, h	4.00 (2.03-25.08)	4.00 (1.00-9.00)	4.00 (2.00-24.93)
AUC_{24h}, ng.h/mL	2714 ± 1535	1792 ± 711	1762 ± 662

[a] Arithmetic mean across subjects.

Assessment of Drug Interactions

Emtricitabine

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving FTC with other medicinal products is low.

FTC is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of FTC with drugs that are eliminated by active tubular secretion may increase concentrations of FTC and/or the coadministered drug.

Drugs that decrease renal function may increase concentrations of FTC.

Rilpivirine

RPV is primarily metabolized by cytochrome CYP3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of RPV. Coadministration of ODEFSEY® and drugs that induce CYP3A may result in decreased plasma concentrations of RPV and loss of virologic response and possible resistance. Coadministration of ODEFSEY® and drugs that inhibit CYP3A may

result in increased plasma concentrations of RPV. Coadministration of ODEFSEY® with drugs that increase gastric pH may result in decreased plasma concentrations of RPV and loss of virologic response and possible resistance to RPV and to the class of NNRTIs.

Tenofovir Alafenamide

TAF is a substrate of P glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption.

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving tenofovir alafenamide with other medicinal products is low.

TAF is not an inhibitor or inducer of CYP3A4 *in vivo*.

Drug Interaction Studies

Drug-drug interaction studies were conducted with ODEFSEY® or the components of ODEFSEY® (FTC, RPV, or TAF) as individual agents.

The effects of coadministered drugs on the exposures of RPV and TAF are shown in Table 12 and Table 13, respectively. The effects of RPV and TAF on the exposure of coadministered drugs are shown in Table 14 and Table 15, respectively.

Table 12. Drug Interactions: Pharmacokinetic Parameters for RPV in the Presence of Coadministered Drugs

Coadministered Drug	Dose/Schedule		N	Mean Ratio of Rilpivirine Pharmacokinetic Parameters With/Without Coadministered Drug (90% CI); No Effect=1.00		
	Coadministered Drug (mg)	Rilpivirine (mg)		C_{max}	AUC	C_{min}
Acetaminophen	500 single dose	150 once daily[a]	16	1.09 (1.01, 1.18)	1.16 (1.10, 1.22)	1.26 (1.16, 1.38)
Atorvastatin	40 once daily	150 once daily[a]	16	0.91 (0.79, 1.06)	0.90 (0.81, 0.99)	0.90 (0.84, 0.96)
Chlorzoxazone	500 single dose taken 2 hours after rilpivirine	150 once daily[a]	16	1.17 (1.08, 1.27)	1.25 (1.16, 1.35)	1.18 (1.09, 1.28)
Ethinylestradiol/ Norethindrone	0.035 once daily/ 1 once daily	25 once daily	15	↔[b]	↔[b]	↔[b]
Famotidine	40 single dose taken 12 hours before rilpivirine	150 single dose[a]	24	0.99 (0.84, 1.16)	0.91 (0.78, 1.07)	NA
Famotidine	40 single dose taken 2 hours before rilpivirine	150 single dose[a]	23	0.15 (0.12, 0.19)	0.24 (0.20, 0.28)	NA
Famotidine	40 single dose taken 4 hours after rilpivirine	150 single dose[a]	24	1.21 (1.06, 1.39)	1.13 (1.01, 1.27)	NA
Ketoconazole	400 once daily	150 once daily[a]	15	1.30 (1.13, 1.48)	1.49 (1.31, 1.70)	1.76 (1.57, 1.97)
Ledipasvir/ Sofosbuvir	90/400 once daily	25 once daily[b]	42	0.97 (0.92, 1.02)	0.95 (0.91, 0.98)	0.93 (0.89, 0.97)
Methadone	60-100 once daily, individualized dose	25 once daily	12	↔[c]	↔[c]	↔[c]

Omeprazole	20 once daily	25 single dose	15	0.30 (0.24, 0.38)	0.35 (0. 28, 0.44)	NA
Rifabutin	300 once daily	25 once daily	18	0.69 (0.62, 0.76)	0.58 (0.52, 0.65)	0.52 (0.46, 0.59)
Rifampin	600 once daily	150 once daily[a]	16	0.31 (0.27, 0.36)	0.20 (0.18, 0.23)	0.11 (0.10, 0.13)
Sildenafil	50 single dose	75 once daily[a]	16	0.92 (0.85, 0.99)	0.98 (0.92, 1.05)	1.04 (0.98, 1.09)
Simeprevir	25 once daily	150 once daily	23	1.04 (0.95, 1.30)	1.12 (1.05, 1.19)	1.25 (1.16, 1.35)
Sofosbuvir/ velpatasvir	400/100 once daily	25 once daily[d]	24	0.93 (0.88, 0.98)	0.95 (0.90, 1.00)	0.96 (0.90, 1.03)
Sofosbuvir/ velpatasvir/ voxilaprevir	400/100/100 + 100 voxilaprevir[e] once daily	25 once daily[c]	30	0.79 (0.74, 0.84)	0.80 (0.76, 0.85)	0.82 (0.77, 0.87)

CI=Confidence Interval; N=maximum number of subjects with data; NA=not available; ↔=no change

[a] This interaction study has been performed with a dose higher than the recommended dose for RPV (25 mg once daily) assessing the maximal effect on the coadministered drug.

[b] Study conducted with ODEFSEY® (FTC/RPV/TAF).

[c] Comparison based on historic controls.

[d] Study conducted with FTC/RPV/TDF

[e] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 13. Drug Interactions: Changes in Pharmacokinetic Parameters for TAF in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI)[b]; No effect=1.00		
				C_{max}	AUC	C_{min}
Cobicistat	150 once daily	8 once daily	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)	NA
Efavirenz[c]	600 once daily	40 once daily[d]	11	0.78 (0.58, 1.05)	0.86 (0.72, 1.02)	NA
Ledipasvir/ Sofosbuvir	90/400 once daily	25 once daily[e]	42	1.03 (0.94, 1.14)	1.32 (1.25, 1.40)	NA
Sofosbuvir/ velpatasvir/ voxilaprevir	400/100/100 + 100 voxilaprevir[f] once daily	25 once daily[e]	30	1.32 (1.17, 1.48)	1.52 (1.43, 1.61)	NA

NA=not available

[a] All interaction studies conducted in healthy volunteers.

[b] All No Effect Boundaries are 70%−143% unless otherwise specified.

[c] A moderate P-gp and CYP3A4 inducer.

[d] Study conducted with FTC/TAF.

[e] Study conducted with ODEFSEY® (FTC/RPV/TAF).

[f] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 14. Drug Interactions: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of RPV

Coadministered Drug	Dose/Schedule		N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters With/Without RPV (90% CI); No Effect=1.00		
	Coadministered Drug (mg)	Rilpivirine (mg)		C_{max}	AUC	C_{min}

Acetaminophen	500 single dose	150 once daily[a]	16	0.97 (0.86, 1.10)	0.92 (0.85, 0.99)	NA
Atorvastatin 2-hydroxy-atorvastatin 4-hydroxy-atorvastatin	40 once daily	150 once daily[a]	16	1.35 (1.08, 1.68) 1.58 (1.33, 1.87) 1.28 (1.15, 1.43)	1.04 (0.97, 1.12) 1.39 (1.29, 1.50) 1.23 (1.13, 1.33)	0.85 (0.69, 1.03) 1.32 (1.10, 1.58) NA
Chlorzoxazone	500 single dose taken 2 hours after rilpivirine	150 once daily[a]	16	0.98 (0.85, 1.13)	1.03 (0.95, 1.13)	NA
Digoxin	0.5 single dose	25 once daily	22	1.06 (0.97, 1.17)	0.98 (0.93, 1.04)[b]	NA
Ethinylestradiol Norethindrone	0.035/1 once daily	25 once daily	17	1.17 (1.06, 1.30) 0.94 (0.83, 1.06)	1.14 (1.10, 1.19) 0.89 (0.84, 0.94)	1.09 (1.03, 1.16) 0.99 (0.90, 1.08)
Ketoconazole	400 once daily	150 once daily[a]	14	0.85 (0.80, 0.90)	0.76 (0.70, 0.82)	0.34 (0.25, 0.46)
Ledipasvir Sofosbuvir GS-331007[d]	90/400 once daily	25 once daily	41	1.01 (0.97, 1.05) 0.96 (0.89, 1.04) 1.08 (1.05, 1.11)	1.02 (0.97, 1.06) 1.05 (1.01, 1.09) 1.08 (1.06, 1.10)	1.02 (0.98, 1.07) NA 1.10 (1.07, 1.12)
R(-) methadone S(+) methadone	60-100 once daily, individualized dose	25 once daily	13	0.86 (0.78, 0.95) 0.87 (0.78, 0.97)	0.84 (0.74, 0.95) 0.84 (0.74, 0.96)	0.78 (0.67, 0.91) 0.79 (0.67, 0.92)
Metformin	850 single dose	25 once daily	20	1.02 (0.95, 1.10)	0.97 (0.90, 1.06)[c]	NA
Rifampin 25-desacetylrifampin	600 once daily	150 once daily[a]	16	1.02 (0.93, 1.12) 1.00 (0.87, 1.15)	0.99 (0.92, 1.07) 0.91 (0.77, 1.07)	NA NA
Sildenafil *N*-desmethyl-sildenafil	50 mg single dose	75 once daily[a]	16	0.93 (0.80, 1.08) 0.90 (0.80, 1.02)	0.97 (0.87, 1.08) 0.92 (0.85, 0.99)[b]	NA NA
Simeprevir	150 once daily	25 once daily	21	1.10 (0.97, 1.26)	1.06 (0.94, 1.19)	0.96 (0.83, 1.11)
Sofosbuvir GS-331007[d] Velpatasvir	400/100 once daily	25 once daily[e]	24	1.09 (0.95, 1.25) 0.96 (0.90, 1.01) 0.96 (0.85, 1.10)	1.16 (1.10, 1.24) 1.04 (1.00, 1.07) 0.99 (0.88, 1.11)	NA 1.12 (1.07, 1.17) 1.02 (0.91, 1.15)
Sofosbuvir GS-331007[d] Velpatasvir Voxilaprevir	400/100/100 + 100 voxilaprevir[f] once daily	25 once daily	30	0.95 (0.86, 1.05) 1.02 (0.98, 1.06) 1.05 (0.96, 1.16) 0.96 (0.84, 1.11)	1.01 (0.97, 1.06) 1.04 (1.01, 1.06) 1.01 (0.94, 1.07) 0.94 (0.84, 1.05)	NA NA 1.01 (0.95, 1.09) 1.02 (0.92, 1.12)

CI=Confidence Interval; N=maximum number of subjects with data; NA=not available

[a] This interaction study has been performed with a dose higher than the recommended dose of RPV (25 mg once daily) assessing the maximal effect on the coadministered drug.

[b] $AUC_{(0\text{-last})}$

[c] N (maximum number of subjects with data for $AUC_{(0\text{-}\infty)}$=15

[d] The predominant circulating nucleoside metabolite of sofosbuvir.

[e] Study conducted with FTC/RPV/TDF.

[f] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 15. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of TAF[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect=1.00		
				C_{max}	AUC	C_{min}
Midazolam[b]	2.5 single dose, orally	25 once daily	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NA
	1 single dose IV			0.99 (0.89, 1.11)	1.08 (1.04, 1.13)	NA
Ledipasvir	90/400 once daily	25 once daily[c]	41	1.01 (0.97, 1.05)	1.02 (0.97, 1.06)	1.02 (0.98, 1.07)
Sofosbuvir				0.96 (0.89, 1.04)	1.05 (1.01, 1.09)	NA
GS-331007[d]				1.08 (1.05, 1.11)	1.08 (1.06, 1.10)	1.10 (1.07, 1.12)
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	25 once daily[e]	15	1.17 (1.07,1.26)	1.12 (1.07,1.17)	1.16 (1.08, 1.24)
Norgestrel				1.10 (1.02, 1.18)	1.09 (1.01, 1.18)	1.11(1.03, 1.20)
Ethinyl estradiol				1.22 (1.15, 1.29)	1.11 (1.07, 1.16)	1.02(0.92, 1.12)
Sofosbuvir	400/100/100 + 100 voxilaprevir[f] once daily	25 once daily[c]	30	0.95 (0.86, 1.05)	1.01 (0.97, 1.06)	NA
GS-331007[d]				1.02 (0.98, 1.06)	1.04 (1.01, 1.06)	NA
Velpatasvir				1.05 (0.96, 1.16)	1.01 (0.94, 1.07)	1.01 (0.95, 1.09)
Voxilaprevir				0.96 (0.84, 1.11)	0.94 (0.84, 1.05)	1.02 (0.92, 1.12)

NA=not available

[a] All interaction studies conducted in healthy volunteers.

[b] A sensitive CYP3A4 substrate.

[c] Study conducted with ODEFSEY®.

[d] The predominant circulating nucleoside metabolite of sofosbuvir.

[e] Study conducted with FTC/TAF.

[f] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

NON-CLINICAL INFORMATION

Emtricitabine

FTC was not mutagenic or clastogenic in conventional genotoxicity assays.

Long-term carcinogenicity studies of FTC in rats and mice did not show any carcinogenicity potential.

Rilpivirine

Animal toxicology studies have been conducted with RPV in mice, rats, rabbits, dogs, and cynomolgus monkeys. The target organs and systems of toxicity were the adrenal cortex and the associated steroid biosynthesis (mouse, rat, dog, cynomolgus monkey), the reproductive organs (female mouse, male and female dog), the liver (mouse, rat, dog), the thyroid and pituitary gland (rat), the kidney (mouse, dog), the hematopoietic system (mouse, rat, dog), and the coagulation system (rat).

In a study conducted in rats, there were no effects on mating or fertility with RPV up to 400 mg/kg/day, a dose of RPV that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. There was no teratogenicity with RPV in rats and rabbits. The exposures at the embryo fetal NOAELs in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily. In a pre- and postnatal development assessment in rats, RPV had no effect on development of offspring during lactation or postweaning when the mothers were dosed up to 400 mg/kg/day.

RPV was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60, and 160 mg/kg/day were administered to mice and doses of 40, 200, 500, and 1500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in mice and rats. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of RPV did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in mice and rats are considered to be rodent specific, associated with liver enzyme induction. A similar mechanism does not exist in humans; hence, these tumors are not relevant for humans. The follicular cell findings are considered to be rat specific, associated with increased clearance of thyroxine and are not considered to be relevant for humans. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to RPV were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg once daily).

RPV has tested negative in the *in vitro* Ames reverse mutation assay, *in vitro* chromosomal aberration assay in human lymphocyte, and *in vitro* clastogenicity mouse lymphoma assay, tested in the absence and presence of a metabolic activation system. RPV did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

Tenofovir Alafenamide

Distribution studies in dogs showed 5.7 to 15-fold higher ^{14}C-radioactivity in lymphoid tissues (iliac, axillary, inguinal and mesenteric lymph nodes, and spleen) 24 hours following administration of an equivalent dose of [^{14}C]-TAF relative to [^{14}C]-TDF.

Nonclinical studies in rats and dogs revealed bone and kidney as the primary target organs of toxicity.

TAF was not mutagenic or clastogenic in conventional genotoxicity assays.

Because there is a lower tenofovir exposure in rats and mice after TAF compared to TDF, carcinogenicity studies were conducted only with TDF. TDF did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumors, considered likely related to high local concentrations in the gastrointestinal tract at the high dose of 600 mg/kg/day. The mechanism of tumor formation in mice and potential relevance for humans are uncertain.

PHARMACEUTICAL INFORMATION

List of Excipients

Tablet Core	Lactose Monohydrate
	Microcrystalline Cellulose
	Povidone
	Polysorbate 20
	Croscarmellose Sodium
	Magnesium Stearate
Film-Coating	Polyvinyl Alcohol
	Titanium Dioxide
	Polyethylene Glycol
	Talc
	Iron Oxide Black

Incompatibilities

Not applicable.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Do not store above 30ºC. Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

Keep out of the sight and reach of children.

Nature and Contents of Container

ODEFSEY® tablets are packaged in white, high density polyethylene (HDPE) bottles and enclosed with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminum foil liner. Each bottle contains desiccant and polyester coil.

Each bottle contains 30 film-coated tablets.

Instructions for Use and Handling and Disposal

No special requirements.

PRODUCT REGISTRANT

Johnson & Johnson International (Singapore) Pte. Ltd.
2 Science Park Drive
#07-13, Ascent
Singapore Science Park 1
Singapore 118222

BATCH RELEASER

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