ODEFSEY® (emtricitabine/rilpivirine/tenofovir alafenamide) tablets

1 PRODUCT NAME

ODEFSEY (emtricitabine/rilpivirine/tenofovir alafenamide)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ODEFSEY is available as tablets. Each tablet contains 200 mg emtricitabine (FTC), 25 mg rilpivirine (RPV), and 25 mg tenofovir alafenamide (TAF).

Contains sugars as lactose.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Each ODEFSEY tablet is capsule shaped, film-coated and gray in colour. Each tablet is debossed with 'GSI' on one side and the number "255" on the other side. The tablets are supplied in bottles with child resistant closures.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ODEFSEY is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA ≤ 100,000 copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of ODEFSEY.

4.2 Dose and Method of Administration

In adults and paediatric patients ≥ 12 years of age and weighing ≥ 35 kg, the dose of ODEFSEY is one tablet taken orally once daily with food.

No data are available on which to make a dose recommendation for children < 12 years of age or weighing < 35 kg.

Elderly: No dose adjustment is required for elderly patients (see section 4.4 Special Warnings and Precautions for Use).

Renal impairment: No dose adjustment of ODEFSEY is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL/min.

ODEFSEY should not be initiated in patients with estimated creatinine clearance below 30 mL/min as there are no data available regarding the use of ODEFSEY in this population.

No data are available to make dose recommendations in paediatric 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) (see section 5.2 – Pharmacokinetic Properties, Patients with Hepatitic Impairment).

Pregnancy and postpartum: Lower exposures of rilpivirine were observed during pregnancy; therefore, viral load should be monitored closely. Alternatively, switching to another ART regimen could be considered (see sections 5.2 Pharmacokinetic Properties and 4.6 Fertility, Pregnancy and Lactation, Use in Pregnancy).

4.3 Contraindications

ODEFSEY is contraindicated in patients with known hypersensitivity to any of the active substances or any other component of the tablets.
Coadministration with the following drugs is contraindicated due to the potential for serious and/or life-threatening events or loss of virologic response and possible resistance to ODEFSEY (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions):

- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin, rifapentine
- Proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole
- Glucocorticoid systemic dexamethasone, except as a single dose treatment
- Herbal products: St. John's wort (*Hypericum perforatum*)

4.4 Special Warnings and Precautions for Use

General

Patients receiving ODEFSEY or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Patients should be advised that antiretroviral therapies, including ODEFSEY, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that ODEFSEY is not a cure for HIV infection.

Virologic Failure and Development of Resistance

Regardless of HIV-1 RNA level at the start of therapy, more RPV-treated patients with CD4+ cell count less than 200 cells/mm^3 at the start of therapy experienced virologic failure compared to patients with CD4+ cell count greater than or equal to 200 cells/mm^3. More RPV-treated patients with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to patients with HIV-1 RNA less than 100,000 copies/mL at the start of therapy.

The observed virologic failure rate in RPV-treated patients conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz. More patients treated with RPV developed lamivudine/FTC associated resistance compared to efavirenz (see section 5.1 Pharmacodynamic Properties, Clinical Trials).

Resistance testing and/or historical resistance data should guide the use of ODEFSEY.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of ODEFSEY, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with ODEFSEY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

HIV and Hepatitis B Virus (HBV) Coinfection

The safety and efficacy of ODEFSEY have not been established in patients coinfected with HBV and HIV-1. Discontinuation of ODEFSEY therapy in patients co-infected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC or TAF components of ODEFSEY. Patients co-infected 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, resumption of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, discontinuation of anti-hepatitis B therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Use with Other Antiretroviral Products

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.
ODEFSEY should not be used in conjunction with protease inhibitors or non-nucleoside reverse transcriptase inhibitors due to potential drug-drug interactions including altered and/or suboptimal pharmacokinetics of ODEFSEY, and/or the coadministered antiretroviral products.

ODEFSEY should not be coadministered with products containing any of the same active components FTC, RPV or TAF, or with products containing lamivudine, tenofovir disoproxil fumarate (TDF), or with adefovir dipivoxil. Caution should be given to prescribing ODEFSEY with

medicinal products that may reduce the exposure of RPV (see section 4.3 Contraindications and section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including RPV and FTC, components of ODEFSEY. 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, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* 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.

Use in Children

The safety, virologic, and immunologic responses in patients who received GENVOYA were evaluated through Week 48 in 50 treatment-naive, HIV-1 infected patients aged 12 to less than 18 years in an open-label trial, Study GS-US-292-0106 (Study 0106). The pharmacokinetics, safety, tolerability, and efficacy of RPV were evaluated through Week 48 in 36 paediatric patients aged 12 to less than 18 years of age and weighing at least 32 kg in a single-arm, open-label trial, Study C213 (see section 5.1 Pharmacodynamic Properties, In Clinical Studies). Pharmacokinetic parameters, evaluated in 24 patients weighing ≥ 35 kg receiving GENVOYA, were similar to adults receiving GENVOYA. The pharmacokinetics of RPV in paediatric patients 12 to less than 18 years of age receiving RPV 25 mg once daily was comparable to that in adults. There was no impact of body weight on RPV pharmacokinetics in paediatric patients in study C213, similar to what was observed in adults (see section 5.2 Pharmacokinetic Properties). See section 4.2 Dose and Method of Administration for dosing recommendations for paediatric patients aged 12 years and older and weighing at least 35 kg. No data are available on which to make a dose recommendation for paediatric patients younger than 12 years or weighing less than 35 kg. The safety profile in adolescent patients who received treatment GENVOYA or RPV was similar to that in adults (see section 4.8 Undesirable Effects).

Use in the Elderly

In general, dose selection for elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In clinical studies, 80 of the 97 patients enrolled aged 65 years and over received FTC+TAF given with EVG+COBI as a fixed-dose combination tablet. No differences in safety or efficacy have been observed between elderly patients and those between 12 and less than 65 years

of age. Clinical studies of RPV did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients (see section 5.2 Pharmacokinetic Properties, In Clinical Studies).

Renal Impairment

Post marketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with tenofovir alafenamide containing products; while most of these cases were characterised by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events.

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.

Prior to or when initiating ODEFSEY, and during treatment with ODEFSEY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue ODEFSEY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

No dose adjustment of ODEFSEY is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL/min. The safety of ODEFSEY has not been established in adult patients with estimated creatinine clearance that declines below 30 mL/min or in paediatric patients with renal impairment (see section 5.2 Pharmacokinetic Properties, Clinical Trials).

The safety, virologic, and immunologic responses of FTC+TAF was evaluated through144 weeks in an open-label clinical study (Study GS-US-292-0012 [0112]) in which 248 HIV-1 infected adult 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 safety data that from patients with normal renal function.

No dose adjustment of RPV is required in patients with mild or moderate renal impairment (see section 5.2 Pharmacokinetic Properties).

ODEFSEY should not be initiated in patients with estimated creatinine clearance below 30 mL/min as there are no data available regarding the use of ODEFSEY in this population (see section 4.2 Dose and Method of Administration).

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. No pharmacokinetic or safety data are available regarding the use of ODEFSEY in patients with severe hepatic impairment (Child-Pugh Class C).

4.5 Interactions with Other Medicines and Other Forms of Interaction

General

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

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*) (see section 4.3 Contraindications).

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 breast cancer resistance protein (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, H2-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 QTc prolongation.

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 section 4.3 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]	↑ RPV ↓ ketoconazole ↑ TAF	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 rifampicin[b] rifapentine	↓ RPV ↓ TAF	Concomitant use of ODEFSEY with rifampicin, 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.
H2-Receptor Antagonists: famotidine[b]	↔ RPV (famotidine taken 12 hours before RPV) ↓ RPV (famotidine taken 2 hours before RPV) ↔ RPV (famotidine taken 4 hours after RPV)	The combination of ODEFSEY and H2-receptor antagonists should be used with caution as coadministration may cause significant decreases in RPV plasma concentrations (increase in gastric pH). H2-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 TAF 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.

Concomitant Drug Class: Drug Name	Effect[a]	Clinical Comment
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 with ODEFSEY

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.

4.6 Fertility, Pregnancy and Lactation

Impairment of Fertility

No reproductive toxicity studies have been conducted with FTC, RPV and TAF in combination.

Emtricitabine: FTC did not affect fertility in male rats or in female and male mice at respective approximate exposures (AUC) of 130 and 50 to 80 times the exposure in humans. The fertility of offspring was unaffected by treatment of mice from early gestation to the end of lactation (50 times the human exposure).

Rilpivirine: 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.

Tenofovir Alafenamide: There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose up to 160 mg/kg/day equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through day seven of gestation.

Use in Pregnancy

Pregnancy Category B3

There are no adequate and well controlled clinical studies of ODEFSEYor its components in pregnant women. Because animal reproductive studies are not always predictive of human

response, ODEFSEYshould be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Emtricitabine: No evidence of embryofoetal toxicity or teratogenicity was observed in mice or rabbits at respective FTC exposures (AUC) of 50 and 130 fold the clinical exposure. Impaired weight gain observed in pregnant rabbits at doses resulting in FTC exposures (AUC) at least 33 times the clinical exposure was not associated with any adverse foetal effects.

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

RPV 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 RPV 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. RPV was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of RPV in HIV-1 infected adults (see section 5.2 Pharmacokinetic Properties).

Placental transfer of RPV or its metabolites from dam to foetus was demonstrated in rats. Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function. There was no clinically relevant teratogenicity with RPV in rats and rabbits. The exposures at the embryofoetal 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.

Tenofovir Alafenamide: Embryofoetal development studies have been performed in rats and rabbits revealed no evidence of embrolethality, fetotoxicity or teratogenicity due to TAF. The embryofoetal NOAELs in rats and rabbits occurred at TAF exposures (AUC) similar to and 53 times higher than, respectively, the exposure in humans at the recommended daily dose.

Use in Lactation

Emtricitabine: In humans, samples of breast milk obtained from five HIV-1 infected mothers given TRUVADA (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: Studies in lactating rats and their offspring indicate that RPV was present in rat milk. 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. Tenofovir-associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with TAF are unknown.

Because of the potential for both HIV-1 transmission and for serious adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving ODEFSEY.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects of ODEFSEY on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/

As ODEFSEY contains FTC, RPV and TAF, adverse reactions associated with these individual antiretroviral agents may be expected to occur with the fixed combination tablet.

For additional safety information about EMTRIVA (FTC), or EDURANT (RPV) in combination with other antiretroviral agents, consult the Product Information for these products.

No data are available from clinical studies of ODEFSEY in HIV-infected patients. The safety of ODEFSEY is based on studies of FTC+TAF when given with EVG+COBI as the fixed-dose combination tablet, GENVOYA (EVG/COBI/FTC/TAF); and studies of RPV when given with FTC+TDF as individual components or as the fixed-dose combination tablet, EVIPLERA.

Clinical Trials

Emtricitabine and 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 [0104] and GS-US-292-0111[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.

The most common adverse reaction (all Grades) and reported in ≥ 10% of patients in the GENVOYA group was nausea. The proportion of patients who discontinued treatment with GENVOYA or STRIBILD due to adverse events, regardless of severity, was 1.3% and 3.3%, respectively. Table 2 displays the frequency of adverse reactions (all Grades) greater than or equal to 5%.

Table 2. Treatment-Emergent Adverse Drug Reactions[a] (All Grades) Reported in ≥ 5% of HIV-1 Infected Treatment-Naïve Adults Receiving GENVOYA in Studies 0104 and 0111 (Week 144 analysis)

	GENVOYA N=866	STRIBILD N=867
GASTROINTESTINAL DISORDERS		
Diarrhoea	7%	9%
Nausea	11%	13%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	5%	4%
NERVOUS SYSTEM DISORDERS		
Headache	6%	5%

a. Frequencies of adverse reactions are based on all adverse events attributed to study drugs by the investigator.

The majority of events presented in Table 2 occurred at severity Grade 1.

In addition to the adverse reactions presented in Table 2, abdominal pain, dyspepsia, flatulence, rash, and vomiting occurred at a common frequency of (≥ 1% and < 10%; frequency based on all adverse events, regardless of relationship to study drug) in the GENVOYA group.

Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3-4) occurring in at least 2% of patients receiving GENVOYA in Studies 0104 and 0111 are presented in Table 3.

Table 3. Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Patients Receiving GENVOYA in Studies 0104 and 0111 (Week 144 analysis)

	GENVOYA N=866	STRIBILD N=867
Laboratory Parameter Abnormality[a]		
Creatine Kinase (≥ 10.0 x ULN)	11%	10%
LDL-cholesterol (fasted) (>190 mg/dL)	11%	5%
Total cholesterol (fasted) (>300 mg/dL)	4%	3%
AST (>5.0 x ULN)	3%	4%
ALT (> 5.0 x ULN)	3%	3%
Amylase (>2.0 x ULN)	3%	5%
Urine RBC (Hematuria) (>75 RBC/HPF)	3%	3%
Lipase[b]	5%	8%

a. Frequencies are based on treatment-emergent laboratory abnormalities.
b. Lipase test was performed only for subjects with serum amylase > 1.5 × upper limit of normal.

Serum Lipids

In the clinical studies of FTC+TAF and FTC+TDF, both given with EVG+COBI as a fixed-dose combination tablet, a similar percentage of patients receiving FTC+TAF and FTC+TDF were on lipid lowering agents at baseline (4% and 5%, respectively). While receiving study drug through Week 144, an additional 5.5% of FTC+TAF patients were started on lipid lowering agents, compared to 5.8% of FTC+TDF patients.

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in Table 16 (see section 5.1 Pharmacodynamic Properties, In Clinical Studies).

Experience from Clinical Studies in Virologically Suppressed Patients

No new adverse reactions to FTC+TAFwere identified through Week 96 in an open-label clinical study (Study GS-US-292-0109 [0109]) of virologically suppressed patients who switched from a TDF-containing combination regimen to FTC+TAF given with EVG+COBI as a fixed-dose combination (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 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 safety data from patients with normal renal function (see section 5.2 Pharmacokinetic Properties).

Experience from Clinical Studies in Paediatric Patients

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

The safety of RPV was evaluated through Week 48 in a single-arm, open-label study (Study C213) in 36 paediatric 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.

Rilpivirine-Containing Regimens

Experience from Clinical Studies in Treatment-Naïve Patients

The safety assessment is based on the Week 96 pooled data from 1368 patients in the controlled Studies C209 and C215 in which 80% of antiretroviral treatment-naïve HIV-1 infected adult patients received RPV 25 mg once daily in combination with other antiretroviral medicinal products (N=550). 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. Adverse reactions observed in these studies were generally consistent with those seen in previous studies of the individual components (Table 4).

The most common adverse reactions (incidence ≥ 3%, Grades 2-4) that occurred in patients receiving FTC/TDF, and RPV in clinical Studies C209 and C215 were depression, insomnia, headache and diarrhoea.

Table 4. Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in > 2% of Patients Receiving RPV or Efavirenz in Combination with FTC/TDF in Studies C209 and C215 (Week 96 Analysis)

	FTC/TDF + RPV	FTC/TDF + Efavirenz
	N=550	N=546
Gastrointestinal Disorder		
Diarrhoea[b]	5%	3%
Nausea	1%	3%
Nervous System Disorders		
Dizziness	1%	7%
Headache	4%	4%
Psychiatric Disorders		
Abnormal dreams	2%	5%
Depression	5%	3%
Insomnia	3%	3%
General Disorders and Administration site disorders		
Fatigue	2%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	3%	10%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
b. Adverse reactions not associated with RPV.

Laboratory Abnormalities: Laboratory abnormalities observed in Studies C209 and C215 were generally consistent with those seen in other studies of the individual components (Table 5).

Table 5. Significant Laboratory Abnormalities (Grades 3-4) Reported in ≥ 1% of Patients Who Received RPV or Efavirenz in Combination with FTC/TDF in Studies C209 and C215 (Week 96 Analysis)

	FTC/TDF + RPV	FTC/TDF + Efavirenz
Hypophosphatemia	1.3% (7/549)	1.9% (10/535)
Pancreatic Amylase (> 2 ULN[a])	4.2% (23/549)	4.9% (26/536)
Lipase (> 3 ULN)	< 1% (5/549)	1.5% (8/536)
AST (> 5 ULN)	2.6% (14/549)	3.6% (19/535)
ALT (> 5 ULN)	1.6% (9/549)	3.5% (19/536)
Total Cholesterol (fasted) (> 300 mg/dL)	< 1% (1/549)	2.2% (12/535)
LDL-Cholesterol (fasted) (> 191 mg/dL)	< 1% (5/549)	3.9% (21/534)
Triglycerides (fasted) (> 751 mg/dL)	< 1% (3/549)	2.6% 14/535)

a. ULN=Upper limit of normal value.

RPV was associated with fewer neurological and psychiatric adverse reactions than efavirenz in patients who received FTC/TDF in Studies C209 and C215.

Additionally, adverse reactions that occurred in up to 2% of patients receiving RPV with other antiretroviral agents in clinical studies include decreased appetite, sleep disorders, abnormal

dreams, depressed mood, somnolence, abdominal pain, vomiting, abdominal discomfort and dizziness.

Adrenal Function: In the pooled Phase 3 Studies of C209 and C215, in patients treated with RPV plus any of the allowed background regimen (N=686), at Week 96, there was an overall mean change from baseline in basal cortisol of -19.1 nmol/L in the RVP group, and an increase of -0.6 nmol/L in the efavirenz group. At Week 96, the mean change from baseline in ACTH stimulated cortisol levels was lower in the RPV group (+18.4 ± 8.36 nmol/L) than in the efavirenz group (+54.1 ± 7.24 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 96 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. Effects on adrenal function were comparable by background N(t)RTIs.

Serum Creatinine*:* In the pooled Phase 3 Studies of C209 and C215 studies in patients treated with RPV plus any of the allowed background regimen (N=686), there was a small increase in serum creatinine over 96 weeks of treatment with RPV. Most of this increase occurred within the first four weeks of treatment; a mean change of 9 µmol/L (range,
-26 µmol/L to 53 µmol/L) was observed through Week 96. In patients who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in patients with normal renal function. These changes are not considered to be clinically relevant, and no patient discontinued treatment due to increases in serum creatinine. Creatinine increases were comparable by background N(t)RTIs.

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 EVIPLERA (FTC/RPV/TDF) to ODEFSEY (Study GS-US-366-1216 [1216], N=316), or from ATRIPLA (EFV/FTC/TDF) to ODEFSEY (Study GS-US-366-1160[1160], N=438). .

Postmarketing Experience

In addition to adverse reactions from clinical studies the following possible adverse reactions have also been identified during post approval use of EVIPLERA or products containing TAF. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

The following adverse reactions have been identified during post approval use of EVIPLERA:

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 post approval use of products containing TAF:

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Angioedema, urticaria

RENAL AND URINARY DISORDERS
Acute renal failure, proximal renal tubulopathy, Fanconi syndrome

4.9 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.

For risk assessment and advice on the management of overdose please contact the National Poisons Information Centre on 131126 (Australia) and 0800 POISON (764 766) (New Zealand).

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study single doses of FTC 1200 mg were administered to 11 patients. No severe adverse reactions were reported. The effects of higher doses are not known. Haemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). 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: Limited clinical experience is available at doses higher than the therapeutic dose of TAF. A single supratherapeutic dose of 125 mg TAF was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations,
ATC code: J05AR19.

Mechanism of Action

ODEFSEY is a fixed dose combination of antiretroviral drugs FTC, RPV, and TAF.

Emtricitabine*:* FTC is a synthetic nucleoside analogue of cytidine, and is phosphorylated by cellular enzymes to form FTC 5'-triphosphate. FTC 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate 2'-deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. FTC 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε and mitochondrial DNA polymerase γ.

Rilpivirine: RPV is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. RPV activity is mediated by non-competitive 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 phosphonamidate 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 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 (HBV). *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..

Antiviral Activity *In Vitro*

Emtricitabine: The *in vitro* antiviral activity of FTC against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and PBMCs. The IC_{50} value for FTC was in the range of 0.0013 to 0.64 μM (0.0003 to 0.158 μg/mL). In drug combination studies of FTC with NRTIs (abacavir, 3TC, d4T, zalcitabine, AZT), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (PI) (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. FTC displayed antiviral activity *in vitro* against HIV-

1 clades A, C, D, E, F, and G (IC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 μM).

Rilpivirine: RPV exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median 50% effective concentration (EC_{50}) value for HIV-1_{IIIB} of 0.73 nM. Although RPV demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2510 to 10830 nM, 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 and group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM. RPV showed additive to synergistic antiviral activity in combination with the N(t)RTIs abacavir, didanosine, FTC, 3TC, d4T, tenofovir, and AZT; 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 sub-types 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.

Drug Resistance

<u>In Cell Culture:</u>

Emtricitabine: FTC-resistant isolates of HIV-1 have been selected in vitro. Genotypic analysis of these isolates showed that the reduced susceptibility to FTC was associated with a mutation in the HIV-1 RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

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 Clinical Studies:

In Treatment-Naïve 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 0104 and 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 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. All patients in both treatment groups who developed resistance mutations to EVG in integrase also developed resistance mutations to FTC in reverse transcriptase.

In phenotypic analyses of patients in the 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 (25%) in the EVG+COBI+FTC+TDF group. One patient in the EVG+COBI+FTC+TAF group (1 of 22 [4.5%]) and 2 patients 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 (C209) and TMC278-C215 (C215) (see section 5.2 Pharmacokinetic Properties, Clinical Trials) (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:

Three subjects with emergent resistance to FTC and/or EVG were identified (M184M/I; M184I + E92G; M184V + E92Q) as of Week 96 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 (Study 0109, N=959).
Rilpivirine-Containing Regimens: Through Week 96, in patients who switched to ODEFSEY from EVIPLERA or ATRIPLA (Studies 1216 and 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 isolates with the M184V/I substitution were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, stavudine, tenofovir, and zidovudone. HIV-1 isolates containing the K65R mutation, selected in vivo by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by FTC. 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 Regimens: 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 C209 and C215 (see section 5.1 Pharmacokinetic Properties, In 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 patients, 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. In the RPV group, 6 patients had HIV-1 with reduced susceptibility to abacavir, 9 with reduced susceptibility to didanosine, 3 with reduced susceptibility to stavudine and 2 with reduced susceptibility to zidovudine.

In Virologically Suppressed Adult Patients

In Study GS-US-264-0106, 4 of the 469 patients that switched from a protease inhibitor-based regimen to EVIPLERA had reduced susceptibility to at least one component of EVIPLERA 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. The effect of the other component, FTC, or the combination of FTC and TAF on the QT interval is not known.

5.2 Pharmacokinetic Properties

Bioequivalence

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

Absorption

Emtricitabine and Tenofovir Alafenamide: Following oral administration with food in HIV-1 infected adult patients, peak plasma concentrations were observed 3 hours post-dose for FTC and 1 hour post-dose for TAF (see Table 6 for additional pharmacokinetic parameters).

Table 6. Pharmacokinetic Parameters of FTC and TAF Exposure Following Oral Administration in HIV-Infected Adults

Parameter Mean ± SD [range: min:max]	FTC[a]	TAF[b]
C_{max} (µg/mL)	1.9 ± 0.5 [0.6:3.6]	0.16 ± 0.08 [0.02:0.97]
AUC_{tau} (µg/h mL)	12.7 ± 4.5 [5.2:34.1]	0.21 ± 0.15 [0.05:1.9]
C_{trough} (µg/mL)	0.14 ± 0.25 [0.04:1.94]	NA

SD = Standard Deviation; NA = Not Applicable

a. From Intensive Pharmacokinetic analysis, N=61-62

b. From Population Pharmacokinetic analysis, N=539.

Emtricitabine*:* Following oral administration of FTC 200 mg capsules, FTC is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following a single oral dose of FTC 200 mg capsules, the plasma FTC half-life is approximately 10 hours.

Rilpivirine: The pharmacokinetic properties of RPV have been evaluated in adult healthy subjects and in adult antiretroviral treatment-naïve HIV-1 infected patients (see Table 7). 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.

Table 7. Population Pharmacokinetic Estimates of RPV 25 mg Once Daily in Antiretroviral Treatment-Naïve HIV-1-infected Adult Patients (Pooled Data from Phase 3 Studies through Week 96)

Parameter	RPV 25 mg Once Daily N=679
AUC_{24h} (ng•h/mL)	
Mean ± SD	2235±851
Median (range)	2096 (198–7307)
C_{0h} (ng/mL)	
Mean ± SD	79±35
Median (range)	73 (2–288)

SD = Standard Deviation

Tenofovir Alafenamide: TAF is rapidly absorbed following oral administration, with peak plasma concentrations occurring at 15−45 minutes post-dose.

Effect of Food on Oral Distribution

Emtricitabine*:* FTC systemic exposure was unaffected when ODEFSEY was administered with food.

Rilpivirine: 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: 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, Metabolism and Elimination

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. *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 faeces (~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.

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: 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. *In vitro* experiments indicate that RPV primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system. 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 faeces and urine, respectively. In faeces, 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: *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 μg/mL. *Ex-vivo* binding of TAF to human plasma proteins in samples collected during clinical studies was approximately 80%. 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. 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, CYP2D6, or UGT1A1. TAF is not an inhibitor or inducer of CYP3A in vivo. 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 to 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.

Pharmacokinetics in Special Populations

Age, Gender and Ethnicity

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

The pharmacokinetics of RPV in antiretroviral treatment-naïve HIV-1 infected paediatric 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 paediatric patients in study C213 (33 to 93 kg), similar to what was observed in adults. Population pharmacokinetic analysis in HIV-1 infected patients showed that RPV pharmacokinetics is not different across the age range (12 to 78 years) evaluated.

Pharmacokinetics of FTC and TAF have not been fully evaluated in the elderly (65 years of age and older). 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 paediatric patients aged 12 to < 18 years were similar to exposures achieved in treatment-naïve adults.

Patients with Hepatic Impairment

Emtricitabine: The pharmacokinetics of FTC have not been studied in patients 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 TAF 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.

Patients with Impaired Renal Function

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

Rilpivirine: The pharmacokinetics of RPV has 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 patients with severe renal impairment (estimated creatinine clearance less than 30 mL/min) in studies of TAF. There are no pharmacokinetic data on TAF in patients with creatinine clearance less than 15 mL/min.

The safety, virologic, and immunologic responses of ODEFSEY in HIV-1 infected patients with mild to moderate renal impairment (eGFR by Cockcroft-Gault method 30 - 69 mL/min) are based on an open label trial (Study 0112) that evaluated FTC+TAF given with EVG+COBI as a fixed dose combination tablet in 242 virologically suppressed patients and 6 treatment naïve patients. The safety profile of FTC+TAF in patients with mild to moderate renal impairment was similar to safety data from patients with normal renal function.

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. Population pharmacokinetic analysis indicated that hepatitis B and/or C virus coinfection had no clinically relevant effect on the exposure to RPV.

Pregnancy and postpartum

The exposure to total RPV after intake of RPV 25 mg once daily as part of an antiretroviral regimen was lower during pregnancy (similar for the 2nd and 3rd trimesters) compared with postpartum (see Table 8). The decrease in unbound (i.e., active) RPV pharmacokinetic parameters during pregnancy compared to postpartum was less pronounced than for total RPV.

In women receiving RPV 25 mg once daily during the 2nd trimester of pregnancy, mean intra-individual values for total RPV 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 8. Pharmacokinetic Results of Total RPV after Administration of RPV 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 RPV[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. 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. In drug interaction studies conducted with FTC, coadministration of FTC and famciclovir had no effect on the C_{max} or AUC of either drug.

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.

Tenofovir alafenamide 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 Tables 9 and 10, respectively. The effects of RPV and TAF on the exposure of coadministered drugs are shown in Tables 11 and 12, respectively.

Table 9. Drug Interactions: Pharmacokinetic Parameters for RPV in the Presence of Coadministered Drugs

Coadministered Drug	Dose/Schedule		N	Mean Ratio of RPV Pharmacokinetic Parameters With/Without Coadministered Drug (90% CI); No Effect=1.00		
	Coadministered Drug (mg)	RPV (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 RPV	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 RPV	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 RPV	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 RPV	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)
Methadone	60-100 once daily individualized dose	25 once daily	12	↔[b]	↔[b]	↔[b]

Coadministered Drug	Dose/Schedule		N	Mean Ratio of RPV Pharmacokinetic Parameters With/Without Coadministered Drug (90% CI); No Effect=1.00		
	Coadministered Drug (mg)	RPV (mg)		C_{max}	AUC	C_{min}
Ledipasvir/ Sofosbuvir	90/400 once daily	25 once daily[c]	42	0.97 (0.92, 1.02)	0.95 (0.91, 0.98)	0.93 (0.89, 0.97)
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)
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)
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)
Sofosbuvir/ velpatasvir	400/100 once daily	10 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 patients with data; NA = not available; ↔ = no change

a. This interaction study has been performed with a dose higher than the recommended dose for EDURANT (25 mg once daily) assessing the maximal effect on the coadministered drug.
b. Comparison based on historic controls.
c. Study conducted with ODEFSEY (FTC/RPV/TAF)
d. Study conducted with EVIPLERA (FTC/RPV/TDF).
e. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 10. Drug Interactions: Changes in Pharmacokinetic Parameters for TAF in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug(mg)	TAF (mg)	N	Mean Ratio of TAF 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)	NC
Efavirenz	600 single dose	40 once daily[d]	11	0.78 (0.58,1.05)	0.86 (0.72,1.02)	NC
Ledipasvir/ Sofosbuvir[e]	90/400 once daily	25 once daily	42	1.03 (0.94, 1.14)	1.32 (1.25, 1.40)	NC
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)	NC

NC Not calculated
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 DESCOVY (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 11. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of RPV

Coadministered Drug	Dose/Schedule		N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters With/Without EDURANT (90% CI); No effect = 1.00		
	Coadministered Drug (mg)	RPV (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	40 once daily	150 once daily[a]	16	1.35 (1.08, 1.68)	1.04 (0.97, 1.12)	0.85 (0.69, 1.03)
2-hydroxy-atorvastatin			16	1.58 (1.33, 1.87)	1.39 (1.29, 1.50)	1.32 (1.10, 1.58)
4-hydroxy-atorvastatin			16	1.28 (1.15, 1.43)	1.23 (1.13, 1.33)	NA
Chlorzoxazone	500 single dose taken 2 hours after RPV	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	0.035 once daily	25 once daily	17	1.17 (1.06, 1.30)	1.14 (1.10, 1.19)	1.09 (1.03, 1.16)

Coadministered Drug	Dose/Schedule		N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters With/Without EDURANT (90% CI); No effect = 1.00		
	Coadministered Drug (mg)	RPV (mg)		C_{max}	AUC	C_{min}
Norethindrone	1 once daily		17	0.94 (0.83, 1.06)	0.89 (0.84, 0.94)	0.99 (0.90, .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	90 once daily	25 once daily	42	1.01 (0.97, 1.05)	1.02 (0.97, 1.06)	1.02 (0.98, 1.07)
Sofosbuvir	400 once daily	25 once daily	41	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)
Velpatasvir	100 once daily	25 once[e] daily	24	0.96 (0.85, 1.10)	0.99 (0.88, 1.11)	1.02 (0.91, 1.15)
Sofosbuvir	400 once daily	25 once[e] daily	24	1.09 (0.95, 1.25)	1.16 (1.10, 1.24)	NA
GS-331007[d]				0.96 (0.90, 1.01)	1.04 (1.00, 1.07)	1.12 (1.07, 1.17)
Sofosbuvir	400 once daily	25 once daily	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	100 once daily	25 once daily	30	1.05 (0.96, 1.16)	1.01 (0.94, 1.07)	1.01 (0.95, 1.09)
Voxilaprevir	100 + 100[f] once daily	25 once daily	30	0.96 (0.84, 1.11)	0.94 (0.84, 1.05)	1.02 (0.92, 1.12)
R(-) methadone	60-100 once daily, individualized dose	25 once daily	13	0.86 (0.78, 0.95)	0.84 (0.74, 0.95)	0.78 (0.67, 0.91)
S(+) methadone			13	0.87 (0.78, 0.97)	0.84 (0.74, 0.96)	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	600 once daily	150 once daily[a]	16	1.02 (0.93, 1.12)	0.99 (0.92, 1.07)	NA
25-desacetylrifampin			16	1.00 (0.87, 1.15)	0.91 (0.77, 1.07)	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)
Sildenafil	50 single dose	75 once daily[a]	16	0.93 (0.80, 1.08)	0.97 (0.87, 1.08)	NA
N-desmethyl-sildenafil			16	0.90 (0.80, 1.02)	0.92 (0.85, 0.99)[b]	NA

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

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

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

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

d. The predominant circulating nucleoside metabolite of sofosbuvir.

e. Study conducted with EVIPLERA (FTC/RPV/TDF).

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

Table 12. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of TAF[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	TAF (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)	1.12 (1.03, 1.22)	NC
	1 single dose, IV			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
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)	NC
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]	29	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 (0.93, 1.12)
Sofosbuvir	400/100/100[f] + 100[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)

NC = Not Calculated

a. All interaction studies conducted in healthy volunteers.
b. A sensitive CYP3A4 substrate.
c. Study conducted with ODEFSEY (FTC/RPV/TAF).
d. The predominant circulating nucleoside metabolite of sofosbuvir.
e. Study conducted with DESCOVY (FTC/TAF).
f. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Clinical Trials

No data are available from clinical studies of ODEFSEY in HIV-infected patients. Clinical efficacy of ODEFSEY was established from studies conducted with FTC+TAF when given with COBI-boosted EVG as a fixed-dose combination (GENVOYA); and from studies of RPV when given with TRUVADA (FTC/TDF) as individual components or as a fixed-dose combination EVIPLERA.

Emtricitabine and Tenofovir Alafenamide-Containing Regimens

Treatment-Naïve and Virologically Suppressed Patients

In both Study 0104 and Study 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 0104 and Study 0111, the mean age was 36 years (range, 18 to 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 to 7.0). The mean baseline CD4+ cell count was 427 cells/mm^3 (range, 0 to 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/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 0109, the efficacy and safety of switching from either ATRIPLA, TRUVADA plus atazanavir (boosted by either COBI or ritonavir), or STRIBILD 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 705 cells/mm^3 (range, 79 to 1951).

Patients were stratified by prior treatment regimen. At screening, 42% of patients were receiving TRUVADA plus atazanavir (boosted by either COBI or ritonavir), 32% of patients were receiving STRIBILD, and 26% of patients were receiving ATRIPLA.

Treatment outcomes of Studies 0104 and 0111 through 48 and 144 weeks are presented in Table 13.

Treatment outcomes of Study 0109 through 48 and 96 weeks are presented in Table 14.

Table 13. Virologic Outcomes of Studies 0104 and 0111at Weeks 48[a] and 144 [b]

	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)
	Week 48		Week 144	
HIV-1 RNA < 50 copies/mL	92%	90%	84%	80%
Treatment Difference	2.0% (95% CI: −0.7% to 4.7%)		4.2% (95% CI = 0.6% to 7.8%)	
HIV-1 RNA ≥ 50 copies/mL[c]	4%	4%	5%	4%
No Virologic Data at Week 48 or 144Window	4%	6%	11%	16%
Discontinued Study Drug Due to AE or Death[d]	1%	2%	1%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[e]	2%	4%	9%	11%
Missing Data During Window but on Study Drug	1%	< 1%	1%	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 ≥ 50 copies/mL in the Week 48 window 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 0104 and 0111, 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 rate of virologic success was similar across patient subgroups (age, gender, race, baseline HIV-1 RNA, or baseline CD4 count).

Table 14. Virologic Outcomes of Study 0109 at Week 48[a] and 96[b]

	FTC+TAF (Administered as GENVOYA) (N=959)	Baseline Regime (N=477)	FTC+TAF (Administered as GENVOYA) (N=959)	Baseline Regime (N=477)
	Week 48		**Week 96**	
HIV-1 RNA < 50 copies/mL	97%	93%	93%	89%
Treatment Difference	4.1% (95% CI: 1.6% to 6.7%)		3.7% (95% CI = 0.4% to 7.0%)	
HIV-1 RNA ≥ 50 copies/mL[c]	1%	1%	2%	2%
No Virologic Data at Week 48 or 96 Window	2%	6%	5%	9%
Discontinued Study Drug Due to AE or Death[d]	1%	1%	1%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[e]	1%	4%	3%	6%
Missing Data During Window but on Study Drug	0%	< 1%	1%	< 1%

a. Week 48 window was between Day 294 and 377 (inclusive).
b. Week 96 window was between Day 630 and 713 (inclusive).
c. Included patients who had ≥ 50 copies/mL in the Week-48 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 Study 0109, switching to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet was superior (p=0.017) in maintaining HIV-1 RNA < 50 copies/mL when compared to patients who stayed on their baseline regimen. At Week 96, in patients who had received ATRIPLA as their prior treatment regimen, 90% (227/251) 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. 86% (108/125) of those who stayed on ATRIPLA; in patients who had received TRUVADA plus boosted atazanavir, 92% (370/402) of those who switched remained suppressed vs. 88% (175/199) of those who stayed on TRUVADA plus boosted atazanavir; in patients who had

received STRIBILD, 96% (293/306) of those who switched remained suppressed vs. 93% (142/153) of those who stayed on STRIBILD.

In Studies 0104 and 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 0109 in virologically suppressed patients, the mean increase from baseline in CD4+ cell count at Week 96 was 60 cells/mm^3 in patients who switched and 42 cells/mm^3 in those who stayed on their baseline regimen.

Bone Mineral Density

Bone mineral density (BMD) from baseline to Week 144 in treatment-naïve patients and from baseline to Week 96 in virologically suppressed patients was assessed by dual-energy x-ray absorptiometry (DEXA) to assess the bone safety of patients receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet. As shown in Table 15, 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, there were increases from baseline in mean BMD at the hip and at the spine in the GENVOYA group as compared with minimal changes from baseline in both parameters in the FTC/TDF+third agent group.

Table 15. Measures of Bone Mineral Density (Week 96 and 144 Analysis)

	Treatment-Naïve Adults in Studies 0104 and 0111			**Virologically Suppressed Adults in Study 0109**		
	FTC+TAF (Administered as GENVOYA)	**FTC+TDF (Administered as STRIBILD)**	**Treatment Difference**	**FTC+TAF (Administered as GENVOYA)**	**Baseline Regimen**	**Treatment Difference**
	Week 144			**Week 96**		
Hip DEXA Analysis	**N=690**	**N=683**		**N=809**	**N=396**	
Mean Percent Change in BMD	−0.8%	−3.4%	2.62% p < 0.001	2.4%	−0.5%	2.9% p < 0.001
Patients with Categorical Change:> 3% Decrease in BMD	28%	55%	--	2%	15%	--
> 3% Increase in BMD	13%	6%		35%	9%	
Patients with No Decrease in BMD	40%	19%	--	82%	43%	--

	Treatment-Naïve Adults in Studies 0104 and 0111			Virologically Suppressed Adults in Study 0109		
	FTC+TAF (Administered as GENVOYA)	**FTC+TDF (Administered as STRIBILD)**	**Treatment Difference**	**FTC+TAF (Administered as GENVOYA)**	**Baseline Regimen**	**Treatment Difference**
	Week 144			**Week 96**		
Lumbar Spine DEXA Analysis	**N=702**	**N=686**		**N=821**	**N=401**	
Mean Percent Change in BMD	−0.9%	−3.0%	2.04% p < 0.001	2.1%	−0.1%	2.2% p < 0.001
Patients with Categorical Change:> 3% Decrease in BMD	30%	49%	--	6%	17%	--
> 3% Increase in BMD	13%	7%		37%	18%	
Patients with No Decrease in BMD	39%	22%	--	75%	47%	--

Renal Laboratory Parameters

In the pooled analysis of Studies 0104 and 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), urinary retinol binding protein (RBP) to creatinine ratio, and 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 patients receiving FTC+TAF and in 45% of patients receiving FTC+TDF ($p=0.027$ for treatment difference).

In virologically suppressed patients in Study 0109, there were decreases from baseline in proteinuria (UPCR), albuminuria (UACR), and tubular proteinuria (urinary RBP to creatinine ratio and 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.

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. As seen in Table 16, 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).

Table 16. Lipid Values, Mean Change from Baseline in Studies 0104 and 0111[a]

	FTC+TAF (Administered as GENVOYA) N=799		**FTC+TDF (Administered as STRIBILD) 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 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/min) 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 to 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. At baseline, median eGFR was 56 mL/min, and 33% of patients had an eGFR of 30 to 49 mL/min. Thirty-five percent of patients were on a treatment regimen that did not contain TDF. The mean baseline CD4+ cell count was 664 cells/mm^3 (range, 126 to 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 patients) maintained HIV-1 RNA < 50 copies/mL 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 0112 are summarized in Table 17.

Table 17. Change from Baseline in Renal Laboratory Tests at Week 144 in Virologically Suppressed Patients with Renal Impairment who Switched to FTC+TAF (Administered as GENVOYA) in Study 0112 (Week 144 Analysis)

	FTC+TAF (Administered as GENVOYA) 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. These included improvements in proteinuria, albuminuria, and tubular proteinuria, as shown in Table 17. 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% of patients had an

improvement in proteinuria as measured by urine dipstick; and median percent change in UPCR and UACR 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 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.

Paediatric Patients

In Study 0106, the efficacy, safety, and pharmacokinetics of FTC+TAF were evaluated in an open-label study, in which HIV-1-infected treatment-naïve adolescents received FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. Fifty patients had a mean age of 15 years (range, 12 to 17), were 44% male, 12% Asian, and 88% Black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/mL, median CD4+ cell count was 456 cells/mm^3 (range, 95 to 1110), and median CD4+% was 23% (range, 7% to 45%). Overall, 22% had baseline plasma HIV-1 RNA > 100,000 copies/mL.

At Week 48, 92% achieved HIV-1RNA < 50 copies/mL, similar to response rates in studies of treatment naïve HIV-1 infected adults. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm^3. Three patients had virologic failure by snapshot at Week 48; no emergent resistance to FTC+TAF was detected through Week 48. Mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for total body less head.

Rilpivirine-Containing Regimens

Treatment-Naïve Patients

Studies C209 and C215

The efficacy of RPV versus efavirenz in combination with FTC/TDF was evaluated in two randomized, double-blind, double-dummy, controlled studies (Study C209 and FTC/TDF subset of Study 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 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 C209 and C215, the mean age was 37 years (range, 18 to 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 to 888) and median baseline plasma HIV-1 RNA was 5 log_{10} copies/mL (range, 2 to 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 18. 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 18. Virologic Outcomes of Randomized Treatment of Studies C209 and C215 in Adults (Pooled Data for Patients Receiving RPV or Efavirenz in Combination with FTC/TDF) at Week 48 and Week 96

	Outcome at Week 48		Outcome at Week 96	
	FTC/TDF + RPV N = 550	**FTC/TDF + Efavirenz N = 546**	**FTC/TDF + RPV N = 550**	**FTC/TDF + Efavirenz N = 546**
Overall Response (HIV-1 RNA < 50 copies/mL [a] [TLOVR[b]])	83% (459/550)	82% (450/546)	77% (423/550)	77% (422/546)
By baseline viral load (copies/mL)				
≤ 100,000	90% (258/288)	85% (217/256)	84% (241/288)	81% (206/255)
> 100,000	77% (201/262)	80% (233/290)	69% (182/262)	74% (216/291)
By CD4 count (cells/mm^2)				
< 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)
Non-response				
Virological Failure[c] (all patients)	9% (52/550)	4% (23/546)	11% (63/550)	5% (28/546)
By baseline viral load (copies/mL)				
≤ 100,000	4% (12/288)	2% (6/256)	6% (17/288)	2% (6/255)
> 100,000	15% (40/262)	6% (17/290)	18% (46/262)	8% (22/291)
By CD4 count (cells/mm^2)				
< 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[d]	5% (27/550)	6% (33/546)	8% (44/550)	9% (48/546)

N=total number of patients per treatment arm.

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

b. ITT TLOVR = Intention to Treat Time to loss of virologic response.

c. 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).

d. e.g. loss to follow up, non-compliance, withdrew consent.

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

Based on the pooled data from the C209 and C215 studies the mean CD4 cell count increase from baseline at Week 96 was 226 cells/mm^3 for RPV plus FTC/TDF-treated patients and 222 cells/mm^3 for efavirenz plus FTC/TDF-treated patients.

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 19. The clinical benefit of these findings has not been demonstrated.

Table 19. Lipid Values Reported in Patients Receiving RPV or Efavirenz in Combination with FTC/TDF in Studies C209 and C215[a] (Week 96)

	N	Pooled Data from the Week 96 Analysis of C209 and C215 Studies			
		FTC/TDF + RPV N=550		FTC/TDF + Efavirenz N=546	
		Baseline	Week 96	Baseline	Week 96
		Mean (nmol/L)	Mean Change[b] (nmol/L)	Mean (nmol/L)	Mean Change[b] (nmol/L)
Total Cholesterol (fasted)	430	4	< 1	4	< 1
HDL-cholesterol (fasted)	429	1	< 1	1	< 1
LDL-cholesterol (fasted)	427	2	< 1	2	< 1
Triglycerides (fasted)	430	3	< 1	3	< 1

a. Excludes patients 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.

Patients Coinfected with Hepatitis B and/or Hepatitis C Virus

In patients coinfected with hepatitis B or C virus receiving RPV in studies C209 and C215, the incidence of hepatic enzyme elevation was higher than in patients receiving RPV who were not coinfected. The same increase was also observed in the efavirenz arm. The pharmacokinetic exposure of RPV in coinfected patients was comparable to that in patients without coinfection.

Virologically Suppressed Patients

In Study 1216, the efficacy and safety of switching from EVIPLERA 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 EVIPLERA 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 EVIPLERA (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 1160, the efficacy and safety of switching from ATRIPLA 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 ATRIPLA 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 ATRIPLA (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 1216 and 1160 are presented in Table 20. At Week 96, switching to ODEFSEY was noninferior in maintaining HIV-1 RNA < 50 copies/mL when compared to patients who stayed on EVIPLERA or on ATRIPLA in respective studies.

Table 20. Virologic Outcomes of Randomized Treatment in Study 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	EVIPLERA	ODEFSEY	EVIPLERA	ODEFSEY	ATRIPLA	ODEFSEY	ATRIPLA
	(N=316)	(N=313)[c]	(N=316)	(N=313)[c]	(N=438)	(N=437)	(N=438)	(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%)	
Virologic Failure[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[d]	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 EVIPLERA prior to screening was excluded from the analysis.
d. Includes 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. 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 Study 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 EVIPLERA.

In Study 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 ATRIPLA.

Bone Mineral Density

In Studies 1216 and 1160, changes in BMD were assessed by DXA in patients who had both baseline and Week 96 measurements (Study 1216: N = 160 and 162 in the ODEFSEY arm, and N = 156 and 158 in the EVIPLERA arm, for hip and spine, respectively; Study 1160: N = 322 and 327 in the ODEFSEY arm, and N=345 and 344 in the ATRIPLA 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 EVIPLERA and ATRIPLA groups. Results are summarized in Table 21.

Table 21. 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	**EVIPLERA**	**Treatment Difference**	**ODEFSEY**	**ATRIPLA**	**Treatment Difference**
Hip DEXA 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	5%	13%	--	5%	18%	--
> 3% Increase in BMD	26%	7%		33%	10%	
Patients with No Decrease (≥ zero % change) in BMD	78%	43%	--	75%	40%	--
Lumbar Spine DEXA 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%	1.58% p < 0.001

	GS-US-366-1216			GS-US-366-1160		
	ODEFSEY	**EVIPLERA**	**Treatment Difference**	**ODEFSEY**	**ATRIPLA**	**Treatment Difference**
Patients with Categorical Change: > 3% Decrease in BMD	4%	24%	--	9%	17%	--
> 3% Increase in BMD	35%	18%		33%	19%	
Patients with No Decrease in BMD	73%	46%	--	71%	52%	--

Renal Laboratory Parameters

In Study 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 EVIPLERA. 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 EVIPLERA groups, respectively ($p < 0.001$ for the differences between treatment groups).

In Study 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 ATRIPLA. 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 ATRIPLA 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 1216 and 1160 are presented in Table 22. These changes were not considered clinically relevant.

Table 22. 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]		EVIPLERA N=314 [n=228]		ODEFSEY N=438 [n=225]		ATRIPLA 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 EVIPLERA group in Study GS-US-366-1216 for LDL-Cholesterol (fasted)
e. [n=226] for ODEFSEY group in Study GS-US-366-1160 for LDL-Cholesterol (fasted)

Paediatric Patients

Study C213

The pharmacokinetics, safety, tolerability, and efficacy of RPV 25 mg once daily, in combination with an investigator-selected background regimen (BR) containing two NRTIs, were evaluated in Study C213, a single-arm, open-label Phase 2 study in antiretroviral treatment-naïve HIV-1 infected paediatric 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 to 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 × 10^6 cells/L (range, 25 to 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 patients [66.7%]), followed by 3TC/TDF (8 patients [22.2%]) and 3TC/AZT (4 patients [11.1%]).

The proportion of responders was higher in patients 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 patients 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 patient discontinued due to an adverse event and 1 patient 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.

5.3 Preclinical Safety Data

Genotoxicity

No genotoxicity studies have been conducted with FTC, RPV and TAF in combination.

Emtricitabine was not mutagenic in bacteria or mouse lymphoma cell assays *in vitro* nor clastogenic in the mouse micronucleus test *in vivo*.

Rilpivirine 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 was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

Carcinogenicity

No carcinogenicity studies have been conducted with FTC, RPV and TAF in combination.

Emtricitabine: In long-term oral carcinogenicity studies conducted with FTC, no drug-related increases in tumour incidence were found in mice at doses up to 750 mg/kg/day (32 times the human systemic exposure (AUC) at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (38 times the human systemic exposure at the therapeutic dose).

Rilpivirine: 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 tumours 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: Because there is a lower tenofovir exposure in rats and mice after TAF compared to TDF, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of TDF for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 10 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 4 times that observed in humans at the therapeutic dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

ODEFSEY tablets contain the following ingredients as excipients:
Tablet core: lactose, microcrystalline cellulose, povidone, Polysorbate 20, croscarmellose sodium, and magnesium stearate.
Film-coating: polyvinyl alcohol (E1203), titanium dioxide (E171), polyethylene glycol, talc (E553b), and iron oxide black (E172).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

3 years

6.4 Special Precautions for Storage

ODEFSEY should be stored below 30 °C.

6.5 Nature and Contents of Container

ODEFSEY is supplied in white high density polyethylene (HDPE) bottles containing 30 tablets and a desiccant, polyester coil and is closed with a child resistant closure.

6.6 Special Precautions for Disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

PRESCRIPTION ONLY MEDICINE

8 SPONSOR

Gilead Sciences (NZ)
c/o Tompkins Wake,
Level 17, 88 Shortland Street,
Auckland , 1010
New Zealand
Tel: 0800 443 933

9 DATE OF FIRST APPROVAL

01 February 2018

10 DATE OF REVISION OF THE TEXT

24 February 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Update wording to align with the current NZ DS Template Explanatory Guide
4.9	Update wording to align with the current NZ DS Template Explanatory Guide
6.3	Extension to shelf life