# NEW ZEALAND DATA SHEET

## 1 DESCOVY® (EMTRICITABINE/TENOFOVIR ALAFENAMIDE) TABLETS

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Emtricitabine (FTC) 200 mg/Tenofovir Alafenamide (TAF) 25 mg,
Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg.

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

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

Each 200/25 mg DESCOVY tablet is rectangular shaped, film-coated and blue in colour. Each tablet is debossed with "GSI" on one side and the number "225" on the other side.

Each 200/10 mg DESCOVY tablet is rectangular shaped, film-coated and gray in colour. Each tablet is debossed with "GSI" on one side and the number "210" on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

DESCOVY is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adults and adolescents aged 12 years and older with body weight at least 35 kg. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of DESCOVY (see section 5.2 Pharmacokinetic Properties).

DESCOVY is not for use in Pre-Exposure Prophylaxis (PrEP).

### 4.2 Dose and Method of Administration

In adults and adolescent patients aged 12 years and older and weighing ≥ 35 kg DESCOVY is taken orally once daily with or without food.

The recommended dose of DESCOVY is 200/25 mg.

If DESCOVY is used in combination with an HIV-1 protease inhibitor (PI) that is administered with either ritonavir or cobicistat (COBI), the recommended dose of DESCOVY is 200/10 mg (see Table 1).

**Table 1. Dose of DESCOVY According to Third Agent in the HIV Treatment Regimen**

| Dose of DESCOVY | Third Agent in HIV Treatment Regimen[a] |
|---|---|
| DESCOVY 200/10 mg once daily | Atazanavir with ritonavir or cobicistat<br>Darunavir with ritonavir or cobicistat[b]<br>Lopinavir with ritonavir |
| DESCOVY 200/25 mg once daily | Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir |

See Section 4.5 Interaction With Other Medicines and Other Forms of Interaction.
Descovy 200/10 mg in combination with darunavir 800 mg and cobicistat 150 mg, administered as a fixed-dose combination tablet, was studied in treatment-naïve patients.

See also section 4.5 Interaction With Other Medicines and Other Forms of Interaction. For specific dosing recommendations for coadministered antiretroviral agents, refer to their respective Data Sheet.

No data are available on which to make a dose recommendation for paediatric patients younger than 12 years or weighing less than 35 kg.

*Elderly:* No dose adjustment is required for elderly patients. In clinical trials, 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.

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

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

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

*Hepatic Impairment*: No dose adjustment of DESCOVY is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DESCOVY has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2 Pharmacokinetic Properties).

## 4.3 Contraindications

DESCOVY is contraindicated in patients with known hypersensitivity to any of the active substances or any other component of the tablets.

Please see Table 2 for Established and Other Potentially Significant Drug Interactions. In addition, prescribing information for any drug coadministered with DESCOVY should be consulted to exclude significant interaction or contraindication.

## 4.4 Special Warnings and Precautions for Use

### General

Patients receiving DESCOVY 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.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of HIV transmission, a residual risk cannot be excluded. Appropriate precautions must continue to be used. Patients should also be informed that DESCOVY is not a cure for HIV infection.

### HIV and Hepatitis B Virus (HBV) Co-infection

Discontinuation of DESCOVY therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC and TAF components of DESCOVY. Patients co-infected with HIV and HBV who discontinue DESCOVY 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

DESCOVY should not be coadministered with products containing any of the same components, TAF or FTC; or with products containing lamivudine or tenofovir disoproxil fumarate (TDF). DESCOVY should not be administered with adefovir dipivoxil.

Data support the use of DESCOVY with HIV-1 protease inhibitors atazanavir, darunavir and lopinavir (see Table 2). For treatment of HIV and hepatitis C co-infection, DESCOVY should not be used in conjunction with protease inhibitors that are inhibitors of cathepsin A (such as the anti-hepatitis C agent boceprevir) due to potential drug-drug interactions including altered and/or suboptimal pharmacokinetics of TAF.

**Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including FTC, a component of DESCOVY. 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 DESCOVY were evaluated through Week 24 in 23 treatment-naïve, HIV-1 infected patients aged 12 to less than 18 years in an open-label trial, study GS-US-292-0106 (Study 0106) (see Clinical Data under section 5.1 Pharmacodynamic Properties).

Pharmacokinetic parameters evaluated in 24 patients weighing ≥ 35 kg were similar to adults receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet (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 of age or weighing less than 35 kg. The safety profile in 24 adolescent patients was similar to that in adults (see section 4.8 Undesirable Effects).

**Use in the Elderly**

In clinical trials, 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.

**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 DESCOVY, and during treatment with DESCOVY 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 DESCOVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

The safety, virologic, and immunologic responses of FTC+TAF was evaluated through 24 weeks in an open-label clinical study GS-US-292-0112 (Study 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 DESCOVY is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL/min.

DESCOVY should not be initiated in patients with estimated creatinine clearance below 30 mL/min as there are no data available regarding the use of DESCOVY in this population (see section 4.2 Dose and Method of Administration). No data are available to make dose recommendations in paediatric patients with renal impairment.

**Hepatic Impairment**

No dose adjustment of DESCOVY is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DESCOVY has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see Clinical Data under section 5.1 Pharmacodynamic Properties and section 5.2 Pharmacokinetic Properties).

**Lactic Acidosis/Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues, including emtricitabine, a component of DESCOVY, and tenofovir disoproxil fumarate, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with DESCOVY 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).

## 4.5 Interaction with Other Medicines and Other Forms of Interaction

### General

As DESCOVY contains FTC any interactions that have been identified with FTC individually may occur with DESCOVY.

### Effects of Concomitant Drugs on the Pharmacokinetics of DESCOVY

TAF, a component of DESCOVY, is transported by P-glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Table 2). 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 DESCOVY and development of resistance. Coadministration of DESCOVY with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF.

### Established and Other Potentially Significant Interactions

Drug interaction information for DESCOVY with potential concomitant drugs is summarised in Table 2. The drug interactions described are based on studies conducted with DESCOVY or the components of DESCOVY (FTC and TAF) as individual agents, or are potential drug interactions that may occur with DESCOVY.

The table is not all-inclusive (see section 4.3 Contraindications).

**Table 2. Established and Other Potentially Significant Drug Interactions[a]**

| Concomitant Drug Class: Drug Name | Effect[b] | Clinical Comment |
|---|---|---|
| **Antiretroviral Agents: Protease Inhibitors (PI)** | | |
| Atazanavir/cobicistat | ↑ tenofovir alafenamide | TAF exposure is expected to increase when atazanavir/cobicistat is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily. |

| Concomitant Drug Class: Drug Name | Effect[b] | Clinical Comment |
|---|---|---|
| Atazanavir/ritonavir[c] | ↑ tenofovir alafenamide | TAF exposure is increased when atazanavir/ritonavir is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily. |
| Darunavir/cobicistat[c] | ↔ tenofovir alafenamide<br>↑ tenofovir | Tenofovir exposure is increased when darunavir/cobicistat is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily. |
| Darunavir/ritonavir[c] | ↔ tenofovir alafenamide<br>↑ tenofovir | Tenofovir exposure is increased when darunavir/ritonavir is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily. |
| Lopinavir/ritonavir[c] | ↑ tenofovir alafenamide | TAF exposure is increased when lopinavir/ritonavir is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily. |
| Tipranavir/ritonavir | ↓ tenofovir alafenamide | TAF exposure may decrease when tipranavir/ritonavir is used in combination with DESCOVY. There are no data available to make dosing recommendations. Coadministration with DESCOVY is not recommended. |
| Other Protease Inhibitors | Effect is unknown | There are no data available to make dosing recommendations for coadministration with other protease inhibitors. |
| **Other Agents** | | |
| **Anticonvulsants:**<br>Carbamazepine<br>Oxcarbazepine<br>Phenobarbital<br>Phenytoin | ↓ tenofovir alafenamide | Coadministration of carbamazepine, oxcarbazepine, phenobarbital, or phenytoin, all of which are P-gp inducers, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered. |
| **Antifungals**:<br>Itraconazole<br>Ketoconazole | ↑ tenofovir alafenamide | Coadministration of itraconazole or ketoconazole, both of which are P-gp inhibitors, may increase plasma concentrations of TAF. No dose adjustment is required. |
| **Antimycobacterial:**<br>Rifabutin<br>Rifampicin<br>Rifapentine | ↓ tenofovir alafenamide | Coadministration of rifampicin, rifabutin, and rifapentine, all of which are P-gp inducers, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of DESCOVY with rifabutin, rifampicin, or rifapentine is not recommended. |
| **Hepatitis C Virus Antiviral Agent:**<br>boceprevir | Effect on boceprevir, or tenofovir alafenamide concentrations unknown | Coadministration with boceprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of tenofovir alafenamide based on *in vitro* data. Coadministration of DESCOVY and boceprevir is not recommended. |

| Concomitant Drug Class: Drug Name | Effect[b] | Clinical Comment |
|---|---|---|
| **Herbal Products:** St. John's wort (*Hypericum perforatum*) | ↓ tenofovir alafenamide | Coadministration of St. John's wort, a P-gp inducer, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance.<br><br>Coadministration of DESCOVY with St. John's wort is not recommended. |

a. This table is not all inclusive.
b. ↑ = increase, ↓ = decrease, ↔ = no effect.
c. Indicates that a drug-drug interaction study was not conducted.

## Drugs Without Clinically Significant Interactions with DESCOVY

Based on drug interaction studies conducted with the components of DESCOVY and the following antiretroviral agents, no clinically significant drug interactions were observed with dolutegravir, efavirenz, famciclovir, ledipasvir/sofosbuvir, rilpivirine, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir. No clinically significant drug interactions are expected when DESCOVY is combined with maraviroc, nevirapine, or raltegravir.

Based on drug interaction studies conducted with the components of DESCOVY, no clinically significant drug interactions were observed when DESCOVY was combined with ethinyl estradiol, midazolam, norgestimate, or sertraline. No clinically significant drug interactions are expected when DESCOVY is combined with buprenorphine, methadone, naloxone, or norbuprenorphine.

### *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 and with TDF, coadministration of FTC and famciclovir had no effect on the $C_{max}$ or AUC of either drug.

***Tenofovir Alafenamide:*** TAF is a substrate of P-gp and breast cancer resistance protein (BCRP). Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption.

TAF is not an inhibitor or inducer of CYP3A *in vivo*.

***Drug Interaction Studies***

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

The effects of coadministered drugs on the exposure of TAF are shown in Table 3. The effects of DESCOVY or its components on the exposure of coadministered drugs are shown in Table 4.

**Table 3. Drug Interactions: Changes in Pharmacokinetic Parameters for TAF in the Presence of the Coadministered Drug[a]**

| Coadministered Drug | Dose of Coadministered Drug (mg) | Tenofovir Alafenamide (mg) | N | Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI)[b]; No Effect = 1.00 | | |
|---|---|---|---|---|---|---|
| | | | | $C_{max}$ | AUC | $C_{min}$ |
| Atazanavir | 300 + 100 ritonavir once daily | 10 once daily[c] | 10 | 1.77 (1.28, 2.44) | 1.91 (1.55, 2.35) | NA |
| Atazanavir | 300 + 150 cobicistat once daily | 10 once daily[c] | 20 | 1.80 (1.49, 2.18) | 1.75 (1.55, 1.98) | NA |
| Carbamazepine | 300 twice daily | 25 once daily[c] | 26 | 0.43 (0.36, 0.51) | 0.45 (0.40, 0.51) | NA |
| Cobicistat | 150 daily | 8 once daily | 12 | 2.83 (2.20, 3.65) | 2.65 (2.29, 3.07) | NA |
| Darunavir | 800 + 150 cobicistat once daily | 25 once daily[c] | 11 | 0.93 (0.72, 1.21)[d] | 0.98 (0.80, 1.19)[d] | NA |
| Darunavir | 800 + 100 ritonavir once daily | 10 once daily[c] | 10 | 1.42 (0.96, 2.09)[e] | 1.06 (0.84, 1.35)[e] | NA |
| Dolutegravir | 50 once daily | 10 once daily[c] | 10 | 1.24 (0.88, 1.74) | 1.19 (0.96, 1.48) | NA |
| Efavirenz | 600 once daily | 40 once daily[c] | 11 | 0.78 (0.58, 1.05) | 0.86 (0.72, 1.02) | NA |
| Ledipasvir/ sofosbuvir | 90/400 once daily | 10 once daily[f] | 30 | 0.90 (0.73, 1.11) | 0.86 (0.78, 0.95) | NA |
| Ledipasvir/ sofosbuvir | 90/400 once daily | 25 once daily[g] | 42 | 1.03 (0.94, 1.14) | 1.32 (1.25, 1.40) | NA |
| Lopinavir | 800/200 ritonavir once daily | 10 once daily[c] | 10 | 2.19 (1.72, 2.79) | 1.47 (1.17, 1.85) | NA |
| Sofosbuvir/ velpatasvir | 400/100 once daily | 10 once daily[f] | 24 | 0.80 (0.68, 0.94) | 0.87 (0.81, 0.94) | NA |
| Sofosbuvir/ velpatasvir/ voxilaprevir | 400/100/100 +100 voxilaprevir[h] once daily | 10 once daily[f] | 29 | 0.79 (0.68, 0.92) | 0.93 (0.85, 1.01) | NA |
| Sofosbuvir/ velpatasvir/ | 400/100/100 +100 | 25 once daily[g] | 30 | 1.32 (1.17, 1.48) | 1.52 (1.43, 1.61) | NA |

| Coadministered Drug | Dose of Coadministered Drug (mg) | Tenofovir Alafenamide (mg) | N | Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI)[b]; No Effect = 1.00 | | |
|---|---|---|---|---|---|---|
| | | | | $C_{max}$ | AUC | $C_{min}$ |
| voxilaprevir | voxilaprevir[h] once daily | | | | | |
| Rilpivirine | 25 once daily | 25 once daily | 17 | 1.01 (0.84, 1.22) | 1.01 (0.94, 1.09) | NA |
| Sertraline | 50 once daily | 10 once daily[f] | 19 | 1.00 (0.86, 1.16) | 0.96 (0.89, 1.03) | NA |

a. NA = Not Available/Not Applicable. All interaction studies conducted in healthy volunteers.
b. All No Effect Boundaries are 70% -143% unless otherwise specified.
c. Study conducted with DESCOVY.
d. Mean ratio of tenofovir PK parameters (90% CI) was 3.16 (3.00, 3.33) for $C_{max}$, 3.24 (3.02, 3.47) for AUC, and 3.21 (2.90, 3.54) for $C_{min}$.
e. Mean ratio of tenofovir PK parameters (90% CI) was 2.42 (1.98, 2.95) for $C_{max}$, 2.43 (2.07, 2.84) for $AUC_{last}$.
f. Study conducted with GENVOYA.
g. Study conducted with ODEFSEY® (emtricitabine/rilpivirine/tenofovir alafenamide).
h. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients

## Table 4. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of TAF[a]

| Coadministered Drug | Dose of Coadministered Drug (mg) | Tenofovir Alafenamide (mg) | N | Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00 | | |
|---|---|---|---|---|---|---|
| | | | | $C_{max}$ | AUC | $C_{min}$ |
| Atazanavir | 300 + 100 ritonavir once daily | 10 once daily[c] | 10 | 0.98 (0.89, 1.07) | 0.99 (0.96, 1.01) | 1.00 (0.96, 1.04) |
| Atazanavir | 300 + 150 cobicistat once daily | 10 once daily[c] | 20 | 0.98 (0.94, 1.02) | 1.06 (1.01, 1.11) | 1.18 (1.06, 1.31) |
| Darunavir | 800 + 150 cobicistat once daily | 25 once daily[c] | 11 | 1.02 (0.96, 1.09) | 0.99 (0.92, 1.07) | 0.97 (0.82, 1.15) |
| Darunavir | 800 + 100 ritonavir once daily | 10 once daily[c] | 10 | 0.99 (0.91, 1.08) | 1.01 (0.96, 1.06) | 1.13 (0.95, 1.34) |
| Dolutegravir | 50 once daily | 10 once daily[c] | 10 | 1.15 (1.04, 1.27) | 1.02 (0.97, 1.08) | 1.05 (0.97, 1.13) |
| Lopinavir | 800/200 ritonavir once daily | 10 once daily[c] | 10 | 1.00 (0.95, 1.06) | 1.00 (0.92, 1.09) | 0.98 (0.85, 1.12) |
| Midazolam[d] | 2.5 once daily, orally | 25 once daily | 18 | 1.02 (0.92, 1.13) | 1.12 (1.03, 1.22) | NA |
| | 1 once daily IV | | | 0.99 (0.89, 1.11) | 1.08 (1.04, 1.14) | NA |
| Ledipasvir | 90/400 once daily | 10 once daily[e] | 30 | 1.65 (1.53, 1.78) | 1.79 (1.64, 1.96) | 1.93 (1.74, 2.15) |

| Coadministered Drug | Dose of Coadministered Drug (mg) | Tenofovir Alafenamide (mg) | N | Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00 | | |
|---|---|---|---|---|---|---|
| | | | | $C_{max}$ | AUC | $C_{min}$ |
| Sofosbuvir | | | | 1.28 (1.13, 1.47) | 1.47 (1.35, 1.59) | NA |
| GS-331007[f] | | | | 1.29 (1.24, 1.35) | 1.48 (1.44, 1.53) | 1.66 (1.60, 1.73) |
| Ledipasvir | 90/400 once daily | 25 once daily[g] | 41 | 1.01 (0.97, 1.05) | 1.02 (0.97, 1.06) | 1.02 (0.98, 1.07) |
| Sofosbuvir | | | | 0.96 (0.89, 1.04) | 1.05 (1.01, 1.09) | NA |
| GS-331007[f] | | | | 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[c] | 15 | 1.17 (1.07,1.26) | 1.12 (1.07,1.17) | 1.16 (1.08, 1.24) |
| Norgestrel | | | | 1.10 (1.02, 1.18) | 1.09 (1.01, 1.18) | 1.11 (1.03, 1.20) |
| Ethinyl estradiol | | | | 1.22 (1.15, 1.29) | 1.11 (1.07, 1.16) | 1.02 (0.92 1.12) |
| Rilpivirine | 25 once daily | 25 once daily | 16 | 0.93 (0.87, 0.99) | 1.01 (0.96, 1.06) | 1.13 (1.04, 1.23) |
| Sertraline | 50 single dose | 10 once daily[e] | 19 | 1.14 (0.94, 1.38) | 1.09 (0.90, 1.32) | NA |
| Sofosbuvir | 400/100 once daily | 10 once daily[e] | 24 | 1.23 (1.07, 1.42) | 1.37 (1.24, 1.52) | NA |
| GS-331007f | | | | 1.29 (1.25, 1.33) | 1.48 (1.43, 1.53) | 1.58 (1.52, 1.65) |
| Velpatasvir | | | | 1.30 (1.17, 1.45) | 1.50 (1.35, 1.66) | 1.60 (1.44, 1.78) |
| Sofosbuvir | 400/100/100 + 100[h] once daily | 10 once daily[e] | 29 | 1.27 (1.09, 1.48) | 1.22 (1.12, 1.32) | NA |
| GS-331007f | | | | 1.28 (1.25, 1.32) | 1.43 (1.39, 1.47) | NA |
| Velpatasvir | | | | 0.96 (0.89, 1.04) | 1.16 (1.06, 1.27) | 1.46 (1.30, 1.64) |
| Voxilaprevir | | | | 1.92 (1.63, 2.26) | 2.71 (2.30, 3.19) | 4.50 (3.68, 5.50) |

| Coadministered Drug | Dose of Coadministered Drug (mg) | Tenofovir Alafenamide (mg) | N | Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00 | | |
|---|---|---|---|---|---|---|
| | | | | $C_{max}$ | AUC | $C_{min}$ |
| Sofosbuvir | 400/100/100 + 100[h] once daily | 25 once daily[g] | 30 | 0.95 (0.86, 1.05) | 1.01 (0.97, 1.06) | NA |
| GS-331007f | | | | 1.02 (0.98, 1.06) | 1.04 (1.01, 1.06) | NA |
| Velpatasvir | | | | 1.05 (0.96, 1.16) | 1.01 (0.94, 1.07) | 1.01 (0.95, 1.09) |
| Voxilaprevir | | | | 0.96 (0.84, 1.11) | 0.94 (0.84, 1.05) | 1.02 (0.92, 1.12) |

NA = Not Available/Not Applicable.
a. All interaction studies conducted in healthy volunteers.
b. All No Effect Boundaries are 70% -143% unless otherwise specified.
c. Study conducted with DESCOVY.
d. A sensitive CYP3A4 substrate.
**e.** Study conducted with GENVOYA.
f. The predominant circulating nucleoside metabolite of sofosbuvir.
**g.** Study conducted with ODEFSEY.
**h.** Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

## 4.6 Fertility, Pregnancy and Lactation

### Impairment of Fertility

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

***Emtricitabine:*** Emtricitabine 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).

***Tenofovir Alafenamide:*** There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose 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 DESCOVY or its components in pregnant women. Because animal reproductive studies are not always predictive of human response, DESCOVY should 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 emtricitabine exposures (AUC) of 50- and 130-fold the clinical exposure. Impaired weight gain observed in pregnant rabbits at doses resulting in emtricitabine exposures (AUC) at least 33 times the clinical exposure was not associated with any adverse foetal effects.

***Tenofovir Alafenamide***: Embryofoetal development studies performed in rats and rabbits revealed no evidence of embryolethality, fetotoxicity or teratogenicity due to TAF. The embryo-foetal No Observed Adverse Effect Levels (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**

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

Because of the potential for both HIV transmission and for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving DESCOVY.

## 4.7 Effects on Ability to Drive and Use Machines

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

## 4.8 Undesirable Effects

As DESCOVY contains FTC, adverse reactions associated with FTC may be expected to occur with the fixed combination tablet.

For additional safety information about EMTRIVA® (FTC), in combination with other antiretroviral agents, consult the Data Sheet.

The safety of DESCOVY is based on studies of FTC+TAF when given with EVG+COBI as the fixed-dose combination tablet GENVOYA® (EVG/COBI/FTC/TAF).

**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 (Study 0104) and GS-US-292-0111 (Study 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 FTC+TAF group was nausea. The proportion of subjects who discontinued treatment with FTC+TAF or FTC+TDF due to adverse events, regardless of severity, was 1.3% and 3.3%, respectively. Table 5 displays the frequency of adverse reactions (all Grades) greater than or equal to 5%.

**Table 5. Adverse Drug Reactions[a] (all Grades) Reported in ≥ 5% of HIV-1 Infected Treatment-Naïve Adults Receiving FTC+TAF (Administered as GENVOYA) in Studies 0104 and 0111 (Week 144 Analysis)**

| | FTC+TAF (Administered as GENVOYA) N=866 | FTC+TDF (Administered as 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 5 occurred at severity Grade 1.

In addition to the adverse reactions presented in Table 5, abdominal pain, dyspepsia, flatulence, rash, and vomiting occurred at a common frequency ( ≥1% and < 10%; frequency based on all adverse events, regardless of relationship to study drug) in the FTC+TAF group.

### Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3-4) occurring in at least 2% of patients receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet in Studies 0104 and 0111 are presented in Table 6.

**Table 6. Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Patients Receiving FTC+TAF in Studies 0104 and 0111 (Week 144 Analysis)**

| | FTC+TAF (Administered as GENVOYA) N=866 | FTC+TDF (Administered as 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 x upper limit of normal

## Serum Lipids

In the clinical trials 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 7.

**Table 7. Lipid Values, Mean Change from Baseline, Reported in Patients Receiving FTC+TAF or FTC+TDF in Studies 0104 and 0111[a] (Week 144 Analysis)**

| | FTC+TAF (Administered as GENVOYA) N=866 | | FTC+TDF (Administered as STRIBILD) N=867 | |
|---|---|---|---|---|
| | **Baseline** | **Week 144** | **Baseline** | **Week 144** |
| | mg/dL | Change[b] | mg/dL | Change[b] |
| Total Cholesterol (fasted) | 162 [N=647] | +31 [N=647] | 165 [N=627] | +14 [N=627] |
| HDL-cholesterol (fasted) | 46 [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. Excludes subjects who received lipid lowering agents during the treatment period.
b. The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 144 values.

### Experience from Clinical Studies in Virologically Suppressed Patients

No new adverse reactions to DESCOVY were identified through Week 96 in an open-label clinical study (GS-US-292-0109 (Study 0109)) of virologically suppressed patients who switched treatment from a TDF-containing combination regimen to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet (N=959).

No new adverse reactions to DESCOVY were identified through Week 48 in a randomised double-blind clinical study (GS-US-311-1089 (Study 1089)) of virologically suppressed patients who switched treatment from a TRUVADA-containing regimen to a DESCOVY-containing regimen (N=333).

### Experience from Clinical Studies in Patients with Renal Impairment

The safety of DESCOVY was evaluated through Week 144 in an open-label clinical study (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 patients with normal renal function (see Clinical Data under section 5.1 Pharmacodynamic Properties).

In 84 renally impaired patients who switched to FTC+TAF given with EVG+COBI as a fixed-dose combination 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, -64 mg/dL in HDL-cholesterol, 0.2 in total cholesterol to HDL ratio, and -22 mg/dL in triglycerides.

**Experience from Clinical Studies in Paediatric Patients**

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

**Postmarketing Experience**

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during post approval use of products containing tenofovir alafenamide (TAF). Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Angioedema, urticaria

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

***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:
https://nzphvc.otago.ac.nz/reporting/

## 4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with DESCOVY 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 information on the management of overdose, contact the Poison Information Centre on 0800 764 766.

***Emtricitabine:*** Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine 200 mg. In one clinical pharmacology study single doses of emtricitabine 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 emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

***Tenofovir Alafenamide***: Limited clinical experience is available at doses higher than the therapeutic dose of TAF. A single supratherapeutic dose of TAF 125 mg was administered to 48 healthy subjects, no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by haemodialysis 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: J05AF30.

**Mechanism of Action**

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

FTC has activity that is specific to HIV-1 and HIV-2 and HBV. FTC triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

***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 HIV-1 and HIV-2 and 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 peripheral blood mononuclear cells. The $EC_{50}$ values for FTC were in the range of 0.0013 to 0.64 μM (0.0003 to 0.158 μg/mL).

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

In drug combination studies of FTC with nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, 3TC, d4T, zalcitabine, AZT), non-nucleoside reverse-transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz, nevirapine), and PIs (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. No antagonism was observed for these combinations.

***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, integrase strand transfer inhibitors (INSTIs), and PIs), additive to synergistic effects were observed. No antagonism was observed for these combinations.

**Drug Resistance**

***In Cell Culture:***

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

***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:*** In a pooled analysis of antiretroviral-naive patients receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet in Phase 3 studies GS-US-292-0104 and GS-US-292-0111, genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA ≥400 copies/mL at confirmed virologic failure, at Week 144, or at time of early study drug discontinuation. As of Week 144, the development of one or more primary FTC, TAF, or EVG resistance-associated mutations was observed in 12 of 22 patients with evaluable genotypic data from paired baseline and EVG+COBI+FTC+TAF treatment-failure isolates (12 of 866 patients [1.4%]) compared with 12 of 20 treatment-failure isolates from patients with evaluable genotypic data in the EVG+COBI+FTC+TDF group (12 of 867 patients [1.4%]). Of the 12 patients with resistance development in the EVG+COBI+FTC+TAF group, the mutations that emerged were M184V/I (N=11) and K65R/N (N=2) in reverse transcriptase and T66T/A/I/V (N=2), E92Q (N=4), Q148Q/R (N=1), and N155H (N=2) in integrase. Of the 12 patients with resistance development in the EVG+COBI+FTC+TDF group, the mutations that emerged were M184V/I (N=9), K65R/N (N=4), and L210W (N=1) in reverse transcriptase and E92Q/V (N=4), Q148R (N=2), and N155H/S (N=3) in integrase. In both treatment groups, most patients who developed resistance mutations to EVG in integrase also developed resistance mutations to FTC in reverse transcriptase

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

***In Virologically Suppressed Patients:*** In a Week 96 analysis of virologically-suppressed patients who switched from TRUVADA to DESCOVY while maintaining their third antiretroviral agent (GS-US-311-1089), 1 of 4 patients analysed in the DESCOVY+third agent group (1 of 333 [0.3%]) developed M184V in reverse transcriptase in the first 48 weeks, with reduced susceptibility to emtricitabine. In the TRUVADA+third agent group, 0 of 3 patients analyzed (0 of 330 [0%]) developed resistance to any components of their regimen.

In a Week 48 analysis of virologically-suppressed patients who switched from ABC/3TC while maintaining their third antiretroviral agent (GS-US-311-1717), 1 of 3 patients analyzed in the DESCOVY+third agent group (1 of 253 [0.4%]) developed the K65K/R resistance mutation in addition to pre-existing M184V but had no phenotypic resistance to TAF (phenotypic resistance to FTC was present). In the ABC/3TC+third agent group, 1 of 1 patient

analyzed (1 of 248 [0.4%]) developed resistance to their third agent (ATV; M46I, I50L, and N88S) in addition to pre-existing reverse transcriptase mutations (multiple TAMs, T69H/N, and M184V) and had phenotypic resistance to FTC and ATV.

In a Week 96 analysis of virologically-suppressed patients who switched from a regimen containing FTC+TDF+third agent to FTC+TAF given with EVG+COBI in a fixed-dose combination tablet (GS-US-292-0109), 3 of 6 patients analyzed in the EVG+COBI+FTC+TAF group (3 of 959 [0.3%]) developed resistance to study drugs (2 with EVG/FTC resistance, M184I + E92G and M184V + E92Q; and 1 with FTC resistance only, M184M/I). In the FTC+TDF+third agent group, 1 of 2 patients analyzed (1 of 477 [0.2%]) developed resistance to all 3 components of the regimen (multiple TAMs + M184V + T66A/E92Q).

**Cross-resistance:**

***Emtricitabine:*** FTC-resistant isolates (M184V/I) were cross-resistant to 3TC but retained sensitivity to didanosine, d4T, tenofovir and AZT.

Viruses harbouring mutations conferring reduced susceptibility to d4T and AZT - 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 mutation or substitutions associated with resistance to NNRTI were susceptible to FTC.

***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 were susceptible to TAF.

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

**Pharmacodynamics**

**Effects on Electrocardiogram**

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.

## Clinical Data

The efficacy and safety of DESCOVY in HIV-1 infected, treatment-naïve adults are based on 144-week data from two randomised, double-blind, active-controlled studies, Study 0104 and Study 0111 (N=1733). The efficacy and safety of DESCOVY in virologically-suppressed HIV-1 infected adults is based on 96-week data from a randomised, open-label, active-controlled study, GS-US-292-0109 (N=1436) and a randomised, double-blind, active-controlled study, Study 1089 (N=663). The efficacy and safety of DESCOVY in HIV-1 infected, virologically-suppressed patients with mild to moderate renal impairment are based on 144-week data from an open-label study, Study 0112 (N=242). The efficacy and safety of DESCOVY in HIV-1 infected, treatment-naïve paediatric patients between the ages of 12 to < 18 years is based on 48-week data from an open-label study, Study 0106 (N=50).

## Treatment-Naïve Patients

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

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

In both studies, patients were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies/mL, greater than 100,000 copies/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).

Treatment outcomes of Studies 0104 and 0111 through 144 weeks are presented in Table 8.

**Table 8. Pooled Virologic Outcomes of Studies 0104 and 0111 at 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 144 Window** | 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% |
| **Proportion (%) of Patients with HIV-1 RNA < 50 copies/mL by Subgroup** | | | | |
| Age | | | | |
| < 50 years | 716/777 (92%) | 680/753 (90%) | 647/777 (83%) | 602/753 (81%) |
| ≥ 50 years | 84/89 (94%) | 104/114 (91%) | 82/89 (92%) | 92/114 (72%) |
| Sex | | | | |
| Male | 674/733 (92%) | 673/740 (91%) | 616/733 (84%) | 603/740 (81%) |
| Female | 126/133 (95%) | 111/127 (87%) | 113/133 (85%) | 91/127 (72%) |
| Race | | | | |
| Black | 197/223 (88%) | 177/213 (83%) | 168/223 (75%) | 152/213 (71%) |
| Nonblack | 603/643 (94%) | 607/654 (93%) | 561/643 (87%) | 542/654 (83%) |
| Baseline Viral Load | | | | |
| ≤ 100,000 copies/mL | 629/670 (94%) | 610/672 (91%) | 567/670 (85%) | 537/672 (80%) |
| > 100,000 copies/mL | 171/196 (87%) | 174/195 (89%) | 162/196 (83%) | 157/195 (81%) |

| | 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 | |
| Baseline CD4+ cell count | | | | |
| < 200 cells/mm$^3$ | 96/112 (86%) | 104/117 (89%) | 93/112 (83%) | 94/117 (80%) |
| ≥ 200 cells/mm$^3$ | 703/753 (93%) | 680/750 (91%) | 635/753 (84%) | 600/750 (80%) |

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 or 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.

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 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).

***Bone Mineral Density****:* In the pooled analysis of Studies 0104 and 0111, bone mineral density (BMD) from baseline to Week 144 was assessed by dual-energy X-ray absorptiometry (DXA) to compare the bone safety of TAF to that of TDF. As shown in Table 9, in patients who had both baseline and Week 144 hip or spine measurements (N=690 and 702 in the FTC+TAF group and N=683 and 686 in the FTC+TDF group) there were smaller decreases in BMD in patients receiving FTC+TAF as compared with FTC+TDF, both given with EVG+COBI as a fixed-dose combination tablet.

**Table 9. Measures of Bone Mineral Density in Studies 0104 and 0111 (Week 144 Analysis)**

| | FTC+TAF (Administered as GENVOYA) | FTC+TDF (Administered as STRIBILD) | Treatment Difference |
|---|---|---|---|
| **Hip DXA Analysis** | N=690 | N=683 | |
| Mean Percent Change in BMD | -0.8% | -3.4% | 2.62%<br>p < 0.001 |
| Subjects with Categorical Change:<br>> 3% Decrease in BMD<br>> 3% Increase in BMD | <br>28%<br>13% | <br>55%<br>6% | <br>--<br> |
| Subjects with No Decrease in BMD | 40% | 19% | -- |
| **Lumbar Spine DXA Analysis** | N=702 | N=686 | |
| Mean Percent Change in BMD | -0.9% | -3.0% | 2.04%<br>p < 0.001 |
| Subjects with Categorical Change:<br>>3% Decrease in BMD<br>>3% Increase in BMD | <br>30%<br>13% | <br>49%<br>7% | <br>--<br> |
| Subjects with No Decrease in BMD | 39% | 22% | -- |

***Changes in Renal Laboratory Tests*:** In the pooled analysis of Studies 0104 and 0111, laboratory tests were performed to compare the effect of TAF, to that of TDF on renal laboratory parameters. As shown in Table 10, statistically significant differences were observed between treatment groups that favored TAF for increases in serum creatinine and changes in proteinuria, including Urine Protein to Creatinine Ratio (UPCR), Urine Albumin to Creatinine Ratio (UACR), urine retinol binding protein (RBP) to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio.

**Table 10. Change from Baseline in Renal Laboratory Tests in Studies 0104 and 0111 (Week 144 Analysis)**

| | FTC+TAF (Administered as GENVOYA) N=866 | FTC+TDF (Administered as STRIBILD) N=867 | Treatmetn Difference |
|---|---|---|---|
| Serum Creatinine (mg/dL)[a] | 0.04 ± 0.12 | 0.07 ± 0.13 | -0.04<br>p < 0.001 |
| Proteinuria by Urine Dipstick[b] | 40% | 45% | p = 0.027 |
| Urine Protein to Creatinine Ratio [UPCR][c] | -10.5% | 25.2% | p < 0.001 |
| Urine Albumin to Creatinine Ratio [UACR][c, d] | -5.2% | 5.2% | p < 0.001 |
| Urine Retinol Binding Protein to Creatinine Ratio[c] | 34.8% | 111% | p < 0.001 |
| Urine Beta-2-Microglobulin to Creatinine Ratio[c] | -25.7% | 53.8% | p < 0.001 |

Mean change ± SD.
Includes all severity grades (1-4).
Median percent change.
Week 96 analysis

**Virologically-Suppressed Patients**

***Study 0109***

In Study 0109, the efficacy and safety of switching from either ATRIPLA® (EFV/FTC/TDF), TRUVADA plus atazanavir (boosted by either COBI or ritonavir), or STRIBILD® (EVG/COBI/FTC/TDF), to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet were evaluated in a randomised, open-label trial 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 randomised 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 79-1951).

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 Study 0109 through 48 and 96 weeks are presented in Table 11.

**Table 11. Virologic Outcomes of Study 0109 at Weeks 48[a] and 96[b]**

| | Week 48 | | Week 96 | |
|---|---|---|---|---|
| | **FTC+TAF (Administered as GENVOYA) (N=959)** | **Baseline Regimen (N=477)** | **FTC+TAF (Administered as GENVOYA) (N = 959)** | **Baseline Regimen (N = 477)** |
| **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% | 7% |
| 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 or Week 96 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.

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.

At Week 96, switching to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet was superior (p=0.017) to staying on a baseline regimen in maintaining HIV-1 RNA <50 copies/mL.

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***: In Study 109, changes in BMD were assessed by DXA in patients who had both baseline and Week 96 measurements (N=809 and 821 in the FTC+TAF given with EVG+COBI arm and N=396 and 401 in patients who remained on their baseline regimen, for hip and spine, respectively). Results are summarized in Table 12.

**Table 12. Measures of Bone Mineral Density in Study 0109 (Week 96 Analysis)**

| | FTC+TAF (Administered as GENVOYA) | Baseline Regimen | Treatment Difference |
|---|---|---|---|
| **Hip DXA Analysis** | **N=809** | **N=396** | |
| Mean Percent Change in BMD | 2.4% | -0.5% | 2.9%<br>p < 0.001 |
| Patients with Categorical Change:<br>> 3% Decrease in BMD<br>> 3% Increase in BMD | <br>2%<br>35% | <br>15%<br>9% | -- |
| Patients with No Decrease (≥ zero % change) in BMD | 82% | 43% | -- |
| **Lumbar Spine DXA Analysis** | **N=821** | **N=401** | |
| Mean Percent Change in BMD | 2.1% | -0.1% | 2.2%<br>p < 0.001 |
| Patients with Categorical Change:<br>> 3% Decrease in BMD<br>> 3% Increase in BMD | <br>6%<br>37% | <br>17%<br>18% | -- |
| Patients with No Decrease (≥ zero % change) in BMD | 75% | 47% | -- |

***Changes in Renal Laboratory Tests***: There were decreases from baseline in proteinuria (UPCR), albuminuria (UACR), and tubular proteinuria (urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio), and other measures of proximal renal tubular dysfunction (including fractional excretion of uric acid [FEUA]) in patients receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet, as compared with increases from baseline in patients who stayed on their FTC+TDF-containing baseline

regimen, collectively indicating the reduced impact of TAF on proximal renal tubular function. At Week 96, -the median percentage change in UPCR was −26% vs. 9%; in UACR it was −14% vs. 11%. At Week 48, the median percentage change in urine RBP to creatinine ratio it was −33% vs. 18%; and in urine beta-2-microglobulin to creatinine ratio it was −52% vs. 19% ($p<0.001$ for all comparisons).

***Study 1089***

In Study 1089, the efficacy and safety of switching from TRUVADA to DESCOVY while maintaining the third antiretroviral agent was evaluated in a randomised, double-blind study of virologically-suppressed HIV-1 infected adults (N=663). Patients must have been stably suppressed (HIV-1 RNA <50 copies/mL) on their baseline regimen for at least 6 months. Patients were randomised in a 1:1 ratio to either switch to DESCOVY while maintaining their third agent at baseline (N=333), or stay on their baseline TRUVADA-containing regimen (N=330). Patients had a mean age of 48 years (range 22-79), 85% were male, 75% were White, and 21% were Black. The mean baseline CD4+ cell count was 679 cells/$mm^3$ (range 79-2201).

Patients were stratified by the class of the third agent in their prior treatment regimen. At baseline, 46% of patients were receiving TRUVADA in combination with a boosted protease inhibitor and 54% of patients were receiving TRUVADA in combination with an unboosted third agent.

Treatment outcomes of Study 1089 through 48 and 96 weeks are presented in Table 13.

**Table 13. Virologic Outcomes of Study 1089 at Weeks 48[a] and 96[b]**

| | Week 48 | | Week 96 | |
|---|---|---|---|---|
| | **DESCOVY Containing Regimen (N=333)** | **TRUVADA Containing Regimen (N=330)** | **DESCOVY Containing Regimen (N=333)** | **TRUVADA Containing Regimen (N=330)** |
| **HIV-1 RNA <50 copies/mL** | 94% | 93% | 89% | 89% |
| Treatment Difference | 1.3% (95% CI: -2.5% to 5.1%) | | -0.5% (95% CI: -5.3% to 4.4%) | |
| **HIV-1 RNA ≥50 copies/mL[c]** | <1% | 2% | 2% | 1% |
| **No Virologic Data at Week 48 or 96 Window** | 5% | 5% | 9% | 10% |
| Discontinued Study Drug Due to AE or Death[d] | 2% | 1% | 2% | 2% |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[e] | 3% | 5% | 7% | 9% |
| Missing Data During Window but on Study Drug | <1% | 0% | 0% | <1% |

Week 48 window was between Day 294 and 377 (inclusive).
Week 96 window between Day 630 and 713 (inclusive).
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.
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.
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.

At Week 96, in patients who received a boosted protease inhibitor, 86% (133/155) of those who switched from TRUVADA to DESCOVY remained suppressed vs. 88% (133/151) of those who stayed on TRUVADA; in patients who received an unboosted third agent, 91% (162/178) of those who switched from TRUVADA to DESCOVY remained suppressed vs. 90% (161/179) of those who stayed on TRUVADA.Switching to a DESCOVY-containing regimen was non-inferior to staying on a baseline TRUVADA-containing regimen in maintaining HIV-1 RNA < 50 copies/mL. The mean increase from baseline in CD4+ cell count at Week 96 was 51 cells/mm$^3$ in patients who switched and 47cells/mm$^3$ in those who stayed on their baseline TRUVADA-containing regimen.

***Bone Mineral Density***: In Study 1089, changes in BMD from baseline to Week 96 were assessed by DXA. Results are summarised in Table 14.

**Table 14. Measures of Bone Mineral Density in Study 1089 (Week 96 Analysis)**

| | DESCOVY Containing Regimen | Baseline TRUVADA Containing Regimen | Treatment Difference |
|---|---|---|---|
| **Hip DXA Analysis** | **N=288** | **N=289** | |
| Mean Percent Change in BMD | 1.9% | -0.3% | 2.18%<br>p < 0.001 |
| Patients with Categorical Change:<br>≥ 3% Decrease in BMD<br>≥ 3% Increase in BMD | <br>6%<br>29% | <br>15%<br>11% | -- |
| Patients with No Decrease (≥ zero % change) in BMD | 79% | 47% | -- |
| **Lumbar Spine DXA Analysis** | **N=287** | **N=292** | |
| Mean Percent Change in BMD | 2.2% | -0.2% | 2.33%<br>p < 0.001 |
| Patients with Categorical Change:<br>≥ 3% Decrease in BMD<br>≥ 3% Increase in BMD | <br>8%<br>40% | <br>19%<br>18% | -- |
| Patients with No Decrease (≥zero % change) in BMD | 72% | 46% | -- |

***Changes in Renal Laboratory Tests:*** There were decreases from baseline in proteinuria and tubular proteinuria in patients receiving a regimen containing DESCOVY, as compared with increases in patients who stayed on a regimen containing TRUVADA at baseline, collectively indicating the reduced impact of TAF on proximal renal tubular function. At Week 96, the median percentage change in UPCR was −26% vs. 3%; in UACR it was 3% vs. 27%; in urine RBP to creatinine ratio it was −4% vs. 43%; and in urine beta-2-microglobulin to creatinine ratio it was −30% vs. 47% (p<0.001 for all comparisons).

**HIV-1 Infected Patients with Renal Impairment**

In Study 0112, the efficacy and safety of FTC+TAF were evaluated in an open-label clinical trial 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+TDF in combination with EVG+COBI as a fixed-dose combination tablet. Patients were virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching.

The mean age was 58 years (range 24-82), with 63 patients (26%) who were ≥ 65 years of age. Seventy-nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirteen percent of patients identified as Hispanic/Latino. At baseline, median eGFR was 56 mL/min, and 33% of patients had an eGFR of 30 to 49 mL/min. The mean baseline CD4+ cell count was 664 cells/mm$^3$ (range 126-1813).

At Week 24, 95% (230/242 patients) maintained HIV-1 RNA < 50 copies/mL after switching to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet. At Week 144, 83.1% (197/237) maintained HIV-1 RNA <50 copies/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 summarised in Table 15.

**Table 15. Change from Baseline in Renal Laboratory Tests at Week 144 in Virologically Suppressed Patients with Renal Impairment who Switched to FTC+TAF 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 Retinol Binding Protein to Creatinine Ratio[c] | -63.8% |
| Urine Beta-2-Microglobulin to Creatinine Ratio[c] | -81.9% |

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

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

In patients whose prior antiretroviral regimen did not include TDF (N=84), mean change from baseline in serum creatinine at Week 144 was 0.01 ± 0.31 mg/dL; 73% 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.

**Paediatric Patients**

In Study 0106, the efficacy, safety, and pharmacokinetics of FTC+TAF were evaluated in an open-label trial, 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 48 weeks, 92% achieved HIV-1 RNA < 50 copies/mL, similar to response rates in trials 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.

## 5.2 Pharmacokinetic Properties

### Solubility

FTC is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25°C. The partition coefficient (*log p*) for emtricitabine is -0.43 and the pKa is 2.65.

TAF is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20°C.

### Bioequivalence

FTC and TAF exposures were bioequivalent when comparing DESCOVY 200/25 mg to GENVOYA 150/150/200/10 mg (fixed-dose combination tablet) following single-dose administration to healthy subjects (N=116) under fed conditions.

FTC and TAF exposures were bioequivalent when comparing DESCOVY 200/10 mg, administered simultaneously with EVG 150 mg and COBI 150 mg, to GENVOYA 150/150/200/10 mg (fixed-dose combination tablet) following single-dose administration to healthy subjects (N=100) under fed conditions.

### Absorption and Bioavailability

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 TAF (see Table 16 for additional pharmacokinetic parameters).

**Table 16. 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.

### Effect of Food on Oral Distribution

Relative to fasting conditions, administration of DESCOVY with a high fat meal (~800 kcal, 50% fat) resulted in a decrease in emtricitabine $C_{max}$ and $AUC_{last}$ of 27% and 9%, respectively; and a decrease in TAF $C_{max}$ (15-37%) and an increase in $AUC_{last}$ (17-77%). These changes are not considered clinically meaningful and DESCOVY can be administered without regard to food.

### Distribution, Metabolism and Elimination

***Emtricitabine:*** *In vitro* binding of FTC to human plasma proteins is < 4% and is independent of concentration over the range of 0.02 to 200 µg/mL. Following administration of radiolabelled FTC approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. FTC is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of EMTRIVA, the plasma emtricitabine half-life is approximately 10 hours.

***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 to 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 *in vitro*. 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 eliminated from the body by the kidneys 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.

**Age, Gender and Ethnicity**

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

Pharmacokinetics of FTC and tenofovir 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 Impaired Renal Function**

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

The safety, virologic, and immunologic responses of DESCOVY 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 DESCOVY in subjects with mild to moderate renal impairment was similar to safety data from patients with normal renal function.

**Patients with Hepatic Impairment**

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

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

**Hepatitis B and/or Hepatitis C Virus Co-infection**

Pharmacokinetics of FTC and TAF have not been fully evaluated in hepatitis B and/or C co-infected patients.

## 5.3 Preclinical Safety Data

**Animal Toxicology**

**Genotoxicity**
No genotoxicity studies have been conducted with FTC and TAF in combination.

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

***Tenofovir Alafenamide:*** TAF 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 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).

***Tenofovir Alafenamide:*** Because there is a lower tenofovir exposure in rats and mice after TAF administration 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

*Tablet core:*

DESCOVY 200/25 mg
Microcrystalline cellulose
Croscarmellose sodium
Magnesium Stearate

DESCOVY 200/10 mg
Microcrystalline cellulose
Croscarmellose sodium
Magnesium Stearate

*Film-coating:*

DESCOVY 200/25 mg
Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol
Talc
Indigo carmine aluminum lake

DESCOVY 200/10 mg
Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol
Talc
Iron oxide black

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf Life

2 years

## 6.4 Special Precautions for Storage

DESCOVY should be stored below 30°C.

## 6.5 Nature and Contents of Container

DESCOVY is supplied in high density polyethylene (HDPE) bottles containing 30 tablets and a silica gel 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/- Grant Thornton New Zealand Limited
L4, 152 Fanshawe Street,
Auckland 1010
New Zealand

Tel: 0800 443 933

# 9 DATE OF FIRST APPROVAL

16 February 2017

## 10 DATE OF REVISION OF THE TEXT

15 March 2022

### Summary table of changes

| Section Changed | Summary of new information |
|---|---|
| 4.4, 4.8 | Addition of renal adverse effects |