Common Drug Review

New Combination Product Submission

June 2017

Drug	Emtricitabine/Rilpivirine/Tenofovir alafenamide (Odefsey)
Indication	A complete regimen for the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) with no known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine (FTC) and with a viral load ≤ 100,000 copies/mL.
Reimbursement request	A complete regimen for the treatment of treatment-naive and virologically suppressed adults infected with HIV-1 with no known mutations associated with resistance to the NNRTI class, tenofovir or FTC, and with a viral load ≤ 100,000 copies/mL.
Dosage form(s)	200 mg emtricitabine/25 mg rilpivirine/25 mg tenofovir alafenamide (tablet)
NOC Date	February 10, 2017
Manufacturer	Gilead Sciences Canada, Inc.

Note: The CDR team has made changes to improve the quality and clarity of the content of the information provided in the fixed-dose combination template.

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TABLE OF CONTENTS

Tables

ABBREVIATIONS

3TC	lamivudine
AE	adverse event
ART	antiretroviral therapy
ARV	antiretroviral
BMD	bone mineral density
CDEC	CADTH Canadian Drug Expert Committee
COBI	cobicistat
CSR	Clinical Study Report
DDIs	drug-drug interactions
DHHS	Department of Health and Human Services
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EVG	elvitegravir
FAS	full analysis set
FTC	emtricitabine
HIV-1	human immunodeficiency virus type 1
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleos(t)ide reverse transcriptase inhibitor
PI	protease inhibitor
PK	pharmacokinetic
PP	per protocol
RCT	randomized controlled trial
RNA	ribonucleic acid
RPV	rilpivirine
SD	standard deviation
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir

EXECUTIVE SUMMARY

Introduction

The current standard of care for HIV management is to treat with highly active antiretroviral therapy (HAART) with the primary goal of achieving and maintaining maximal suppression of viral load, which leads to restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.[1]

FTC/RPV/TAF is a three-drug single tablet regimen (STR) product consisting of the following:

- 25 mg rilpivirine (RPV) a non-nucleoside reverse-transcriptase inhibitor (NNRTI)
- 200 mg emtricitabine (FTC) a nucleos(t)ide reverse transcriptase inhibitor (NRTI)
- 25 mg tenofovir alafenamide (TAF) an NRTI

The recommended dose of FTC/RPV/TAF is one tablet taken orally once daily with food.[2] The product monograph states that FTC/RPV/TAF must be taken with a meal to obtain optimal absorption of RPV.[2]

FTC/RPV/TAF is indicated as a complete regimen for the treatment of adults infected with HIV-1 with no known mutations associated with resistance to the NNRTI class, tenofovir or FTC, and with a viral load of ≤ 100,000 copies/mL.[2] The product monograph states that the safety and efficacy of FTC/RPV/TAF has not been established in patients with a prior history of virologic failure.[2] The indications and clinical use section of the product monograph also states that the following points should be considered prior to the initiation of therapy in treatment-naive patients: regardless of HIV-1 RNA at the start of therapy, more rilpivirine-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; the observed virologic failure rate in rilpivirine-treated patients conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to the control (efavirenz); and, more patients treated with rilpivirine developed tenofovir and lamivudine/emtricitabine associated resistance compared to the control.[2]

This submission for FTC/RPV/TAF was filed as a new combination product (funded-components) based on the fact the rilpivirine is funded by a majority of the CDR-participating drug plans and FTC/TAF (Descovy) received a recommendation from the Canadian Drug Expert Committee (CDEC) to reimburse with conditions in August 2016. Therefore, the objective of this review is to conduct an appraisal of the clinical evidence and pharmacoeconomic evaluation filed by the manufacturer.

Included Studies

The manufacturer's submission included a summary of one pivotal bioequivalence study (Study 1159 [N = 96]) that compared the individual components of FTC/RPV/TAF against the individual components of two reference products: EVG/COBI/FTC/TAF (Genvoya) and RPV (Edurant). As shown in Table 1, the results of the bioequivalence study were used to bridge the efficacy and safety data of Edurant, Genvoya, and Complera to support market authorization of FTC/RPV/TAF.

TABLE 1: APPROACH TO BRIDGING BIOEQUIVALENCE DATA WITH EFFICACY AND SAFETY DATA

FTC/RPV/TAF Components	Regimens used for Bioequivalence Studies	Bridged Efficacy and Safety Data
RPV 25 mg	RPV 25 mg (Edurant)	RPV (Edurant) EVG/COBI/FTC/TAF (Genvoya) FTC/RPV/TDF (Complera)
FTC 200 mg	EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg (Genvoya)	
TAF 25 mg		

COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

The efficacy data provided in the manufacturer's submission were derived from seven completed phase III studies and interim data from two phase IIIb studies. The phase three randomized controlled trials were all conducted using products other than FTC/RPV/TAF and included the following: four trials conducted using EVG/COBI/FTC/TAF (Genvoya), including two studies comparing EVG/COBI/FTC/TAF (Genvoya) with EVG/COBI/FTC/TDF (Stribild) in treatment-naive patients (Study 104 [N = 872] and Study 111 [N = 872]), one trial comparing Genvoya with TDF/FTC plus a third agent (Study 109 [N = 1443]) in virologically supressed adults, and one uncontrolled trial conducted in adults with mild to moderate renal failure (Study 112 [N = 248]); two phase III studies comparing RPV (Edurant) with EFV in combination with FTC/TDF (ECHO [N = 694]) or FTC/TDF, AZT/3TC or ABC/3TC (THRIVE [N = 680]); one phase three switching study compared FTC/RPV/TDF (Complera) with the patient's prior treatment regimen (SPIRIT [N = 476]).

The two phase IIIb studies evaluated switching to FTC/RPV/TAF from FTC/RPV/TDF (Study 1216 [N = 632]) or EFV/TDF/FTC (Study 1160 [N = 881]). The primary efficacy end point of both studies was the proportion of patients with HIV 1 RNA < 50 copies/mL at week 48, as defined by the US FDA–defined snapshot algorithm (noninferiority margin of 8%). The CDR submission included interim 48-week data; however, both studies are planned for 96-weeks of follow-up. The manufacturer reported that the results for these studies were not available at the time of the Health Canada submission; therefore, no efficacy or safety data were available from RCTs of FTC/RPV/TAF in HIV-infected patients at the time of regulatory filing. The indications for use in treatment-naive and virologically suppressed patients are based on the efficacy demonstrated in the phase three studies that were conducted using Genvoya, Edurant, and Complera.

Bioequivalence

Study 1159 compared the individual components of FTC/RPV/TAF against EVG/COBI/FTC/TAF (Genvoya) and RPV (Edurant). This approach was used because exposure to TAF results in lower levels of plasma of tenofovir (TFV) compared with TDF;[3] hence, a comparison with a product such as FTC/RPV/TDF (Complera) would be inappropriate. Reviewers for Health Canada concluded that the bioavailability of FTC, TAF, and RPV following administration of the Odefsey tablets is comparable to the bioavailability of FTC and TAF following administration of Genvoya and RPV following administration Edurant.[4,5] Reviewers for the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) indicated that bioequivalence criteria were met for each of the individual components (i.e., FTC, RPV, and TAF).[6,7] Reviewers for the EMA noted that there is no evidence to suggest that exposure to TDF instead of TAF would increase a patient's risk of viral resistance.[6]

Efficacy

As shown in Table 2, the majority of the phase III studies that were included in the review have been previously reviewed by CADTH in the CDR submissions for Genvoya, Descovy, and Edurant.[8-11] All three of these reference products received recommendations from the Canadian Drug Expert Committee (CDEC) to list or list with a condition.[9-11] The two phase IIIb studies evaluated switching to FTC/RPV/TAF from FTC/RPV/TDF (Study 1216 [N = 632]) or EFV/TDF/FTC (Study 1160 [N = 881]). Studies 1160 and 1216 demonstrated that switching to FTC/RPV/TAF was noninferior to remaining on treatment with Atripla or Complera (respectively) for virologic success at 48 weeks.[12,13]

TABLE 2: PHASE III STUDIES INCLUDED IN FTC/RPV/TAF SUBMISSION

Population/Objective	Phase III Studies in Report	Previous CDR Review
ART-Naive Adults	GS-US-292-0104	Genvoya, Descovy
	GS-US-292-0111	Genvoya, Descovy
	ECHO	Edurant, Complera
	THRIVE	Edurant
Virologically Suppressed Adults	GS-US-292-0109	Genvoya, Descovy
Mild to Moderate Renal Impairment	GS-US-292-0112	Genvoya, Descovy
Switching studies	GS-US-366-1216	New study
	GS-US-366-1160	New study
	SPIRIT	Not reviewed in Complera

ART = Antiretroviral Therapy

Harms

Percentage change from baseline in hip and spine bone mineral density (BMD) were pre-specified key secondary endpoints in both studies 1160 and 1216. At the 48-week interim analysis, both studies demonstrated a statistically significant improvement from baseline in BMD at the hip and spine in patients who switched from Complera or Atripla to FTC/RPV/TAF compared with those who continued to be treated with Complera or Atripla ($P < 0.001$ for spine and hip BMD in both studies). In Study 1160, mean percentage changes from baseline to 48 weeks in hip BMD were 1.28% (SD 2.38%) for patients who switched to FTC/RPV/TAF and −0.13% (SD 2.49%) for patients who remained on Atripla; mean (SD) percentage changes from baseline to 48 weeks in spine BMD were 1.65% (SD 3.32%) and −0.05% (SD 2.91%) for FTC/RPV/TAF and Atripla, respectively. In Study 1216, mean (SD) percentage changes in hip BMD at 48 weeks were 1.04% (1.94%) for FTC/RPV/TAF and −0.25% (2.08%) for Complera. For spine BMD mean percentage changes were 1.61% (SD 3.44%) for FTC/RPV/TAF and 0.08% (SD 2.96%) for Complera. The product monograph for FTC/RPV/TAF states that the effects of TAF-associated changes in BMD on long-term bone health and future fracture risk are unknown.[2] Recommendations for BMD monitoring are similar in the product monographs for FTC/RPV/TAF, Complera, and Atripla, indicating that monitoring should be considered for patients who have a history of pathologic bone fracture or are at risk for osteopenia.[2,14,15]

There was also a significant difference in change from baseline in estimated glomerular filtration rate (eGFR) favouring FTC/RPV/TAF over Complera at 48 weeks in Study 1216.[13] In contrast, there was a statistically significant decrease in eGFR for patients who switched from Atripla to FTC/RPV/TAF at 48 weeks in Study 1160.[12] The manufacturer reported that this decrease was likely associated with the initiation of treatment involving RPV, which is not a component of Atripla, and is known to reduce

tubular secretion of creatinine. Compared with Atripla and Complera, the manufacturer reported that patients who switched to FTC/RPV/TAF demonstrated statistically significant reductions in proteinuria, albuminuria, and tubular proteinuria. Patients require the use of HIV antiviral treatment for their lifetime and indicated that they value the improved safety profile of TAF-containing regimens compared with TDF-containing regimens, with respect to fewer renal adverse events and a reduction in the loss of BMD.

Potential Place in Therapy[1]

In Canada, there are some thirty licensed individual or co-formulated HIV antivirals.[16] The majority of patients being treated for HIV will have a more or less "wild type" virus, that is, one that is generally free of drug resistance mutations and therefore will respond to most available antivirals.[17]

The selection of the most appropriate treatment for patients is individualized based on patient lifestyle, tolerance, and virus type. The clinical expert consulted by CADTH for this review indicated that there are practice variabilities across Canada based on physician experience with the available agents, however, the ideal combinations are potent (effectively suppress HIV replication), convenient (STRs versus multi-tablet regimens, once daily dosing, no food requirements), and tolerable in the short and long term.[18] STRs are preferred by most patients, and likely improve adherence and therefore effectiveness. There are five STRs available in Canada: Atripla, Complera, Stribild, Genvoya, and Triumeq. Atripla, Complera and Stribild include TDF, and may therefore be considered less favourable due to their potential for long term renal dysfunction and BMD loss. Genvoya contains TAF instead of TDF, and consequently has less potential for these toxicities; however, Genvoya has numerous drug-drug interactions (DDIs) and should be taken with food. Triumeq does not contain tenofovir, so the renal and bone toxicities are not a concern, it is very tolerable, can be taken with or without food, and has almost no DDIs. However, a small proportion of patients[19] will experience a hypersensitivity reaction to the abacavir component of Triumeq, and concerns remain about the potential cardiotoxicity of abacavir.[20,21]

Treatment for patients in the form of multi-tablet regimens may also be considered. Isentress, Edurant and Tivicay are all free of most DDIs, and have been found to be effective and tolerable. Used in combination with Descovy, there would be few expected short or long term side effects; used in combination with Kivexa, the major consideration would be the potential for cardiotoxicity. Finally, Prezcobix also may be used with Descovy or Kivexa, however, these combinations have the potential for DDIs.

In summary, it can be seen that there are many options for therapy for wild type HIV.
FTC/RPV/TAF has its advantages, but it does not fill any major unmet need. It would most likely be used in substitution for Complera.

Cost

At the submitted daily price of $42.37 per tablet, FTC/RPV/TAF is less costly than the sum of its individual components RPV ($15.14 daily) and FTC/TAF ($28.57 daily), and would therefore result in approximate savings of $1 daily. In addition, FTC/RPV/TAF is less costly than other DHHS-alternative STRs, with daily cost savings ranging from $1.74 (compared to FTC/RPV/TDF) to $2.19 (compared to EFV/FTC/TDF).

[1] This information is based on information provided in draft form by the clinical expert consulted by CADTH for the purpose of this review.

Conclusion

FTC/RPV/TAF is indicated as a complete regimen for the treatment of adults infected with HIV-1 with no known mutations associated with resistance to the NNRTI class, tenofovir or FTC, and with a viral load of ≤ 100,000 copies/mL. The manufacturer's submission included a summary of one pivotal bioequivalence study (Study 1159 [N = 96]) which demonstrated that the individual components of FTC/RPV/TAF were bioequivalent to the individual components of two reference products: EVG/COBI/FTC/TAF (Genvoya) and RPV (Edurant). The results of the bioequivalence study were used to bridge the efficacy and safety data of Edurant, Genvoya, and Complera to support market authorization of FTC/RPV/TAF.

The efficacy data provided in the manufacturer's submission were derived from seven completed phase III studies and interim data from two phase IIIb studies. The majority of the phase III studies that were included in the review have been previously reviewed by CADTH in the CDR submissions for Genvoya, Descovy, and Edurant. The two phase IIIb studies evaluated switching to FTC/RPV/TAF from FTC/RPV/TDF (Study 1216 [N = 632]) or EFV/TDF/FTC (Study 1160 [N = 881]). Studies 1160 and 1216 demonstrated that switching to FTC/RPV/TAF was noninferior to remaining on treatment with Atripla or Complera (respectively) for virologic success at 48 weeks.

Percentage change from baseline in hip and spine bone mineral density (BMD) were pre-specified key secondary endpoints in both studies 1160 and 1216. At the 48-week interim analysis, both studies demonstrated a statistically significant improvement from baseline in BMD at the hip and spine in patients who switched from Complera or Atripla to FTC/RPV/TAF compared with those who continued to be treated with Complera or Atripla ($P < 0.001$ for spine and hip BMD in both studies). The effects of TAF-associated changes in BMD on long-term bone health and future fracture risk are currently unknown.

At the submitted daily price of $42.37 per tablet, FTC/RPV/TAF is less costly than the sum of its individual components, RPV ($15.14 daily) and FTC/TAF ($28.57 daily), and is less costly than other DHHS-alternative STRs, including FTC/RPV/TDF ($44.11 daily).

1. PRODUCT INFORMATION

1.1 Health Canada–Anticipated Indication

Indication to be Reviewed by CDR
A complete regimen for the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) with no known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir (TFV) or emtricitabine (FTC) and with a viral load ≤ 100,000 copies/mL.

1.2 Requested Listing Criteria

Requested Listing Criteria
Gilead Sciences Canada, Inc. is requesting that FTC/rilpivirine (RPV)/tenofovir alafenamide fumarate (TAF) be listed on CADTH Common Drug Review (CDR)–participating drug plans as a complete regimen for the treatment of treatment-naive and virologically suppressed adults infected with HIV-1 with no known mutations associated with resistance to the NNRTI class, TFV or FTC, and with a viral load ≤ 100,000 copies/mL.

1.3 Manufacturer's Rationale and Place in Therapy for the Combination

1.3.1 Rationale

FTC/RPV/TAF is a three-drug single-tablet regimen (STR) product consisting of a NNRTI, RPV 25 mg, a nucleos(t)ide reverse transcriptase inhibitor (NRTI), FTC 200 mg, and a novel NRTI — TAF 25 mg. FTC/RPV/TAF is a convenient once-daily STR offering a number of benefits over existing treatments, including its components.

FTC/RPV/TAF includes the components of Complera, with the exception of the replacement of tenofovir disoproxil fumarate (TDF) 300 mg with TAF 25 mg. Complera is an alternative regimen for HIV-1 treatment in the US Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.[1] Complera first received a positive CADTH Canadian Drug Expert Committee (CDEC) recommendation in April 2012 and is currently widely reimbursed by provincial drug plans across Canada.

With the success of antiretroviral therapy (ART) in reducing HIV-related morbidity and mortality, the life expectancy of patients with HIV has increased, reaching similar levels to that of the general population.[2] As patients with HIV infection live longer and receive ART for several decades, they are exposed to a prolonged risk of HIV and ART–associated as well as non-HIV-related comorbidities.[3-5] Compared to the general HIV-negative population, patients with HIV are at an increased risk of and have a high prevalence of cardiovascular disease, chronic kidney disease, osteopenia/osteoporosis, fractures, malignancies, and neuropsychiatric disease. The long-term effect of ART-related toxicity further increases the risk and severity of experiencing non–HIV-related comorbidities such as cardiovascular disease, chronic kidney disease, and osteopenia/osteoporosis.[2,6-9] Thus, clinical attention has become more focused on the optimization of tolerability and long-term safety of modern ART regimens.[10]

TDF, a component of the most widely prescribed dual NRTI backbone (FTC/TDF; Truvada), is associated with an increased risk of chronic kidney disease[1,11] and a reduction in bone mineral density (BMD).[12] To minimize these "off-target" effects of TDF, Gilead developed TAF, a novel prodrug of TFV that efficiently targets lymphocytes resulting in increased TFV concentrations at the principal site of HIV infection (greater than four-fold higher in peripheral blood mononuclear cells) and greater than 90% lower concentrations of TFV in the plasma, compared to TDF.[13-15] TAF maintains the high levels of efficacy

observed with TDF by reducing the viral load in lymphocytes while minimizing off-target effects associated with higher levels of TFV in the plasma that occur with TDF.[15]

TAF has been co-formulated with FTC as Descovy (200 mg/25 mg and 200 mg/10 mg), a new dual NRTI backbone that is approved by Health Canada for use in combination with other antiretrovirals (ARVs) (such as NNRTIs, protease inhibitors [PIs] or integrase strand transfer inhibitors) for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older (and weighing ≥ 35 kg),[16] and received a positive CDEC recommendation in August 2016.[17] Several studies have demonstrated the enhanced renal and bone safety of Descovy compared with Truvada,[18] and Descovy was recently added to the US DHHS and International Antiviral Society (IAS) guidelines as a recommended dual NRTI backbone for use with a third agent antiviral.[1,19] The choice of third agent should be guided by efficacy, genetic barrier to resistance, adverse event (AE) profile, dosing convenience, non-HIV-related comorbidities, concomitant medications, and the potential for drug-drug interactions (DDIs).[1]

NNRTIs are widely used in the treatment of HIV-1 infection. RPV (Edurant) is a NNRTI that is approved as a single agent for use in combination with other ARV agents for the treatment of HIV-1 infection in treatment-naive patients with HIV-1 ribonucleic acid (RNA) ≤ 100,000 copies/mL at the start of therapy.[20] RPV has an improved safety profile compared with other approved NNRTIs in Canada, including nevirapine (Viramune), delavirdine (Rescriptor), etravirine (Intelence) and efavirenz (EFV; Sustiva), as these NNRTIs are associated with hepatotoxicity, central nervous system symptoms, and/or the risk of teratogenicity.[1] RPV also has a lower potential for DDIs than other NNRTIs.

Complicated HIV treatment regimens demanding a high pill burden and frequent administration may incur higher rates of treatment nonadherence and discontinuation. Adherence to ART has been strongly correlated with HIV viral suppression, reduced rates of antiviral drug resistance, increased survival, and improved quality of life. Current treatment guidelines recommend the use of STRs over multi-tablet regimens as a way to simplify treatment regimens aimed at reducing pill burden and improving patient adherence.[1] STRs also prevent partial adherence, whereby patients take only some components of a multi-tablet regimen, which increases the risk for developing antiviral drug resistance. Also, the use of STRs is known to optimize patient-reported outcomes.[21]

FTC/RPV/TAF is an STR that addresses the need for a highly efficacious, once-daily, complete regimen that combines a recommended dual NRTI backbone, FTC/TAF, that has improved renal and bone safety profiles compared with TDF-containing backbones, with an NNRTI, RPV, that has established safety and tolerability benefits compared with other NNRTIs.

1.3.2 Place in Therapy

FTC/RPV/TAF is currently approved in Europe and the US, and FTC/RPV/TAF was recently added to the US DHHS guidelines as an alternative regimen; alternative regimens may be the preferred regimen for some patients.[1] FTC/RPV/TAF addresses the diverse and evolving needs of treatment-naive and virologically suppressed HIV patients with susceptible strains of HIV-1. The expected place in therapy for FTC/RPV/TAF is in patients for whom an NNRTI-based regimen is most appropriate and who will benefit from the enhanced renal and bone safety profile of a TAF-based rather than a TDF-based regimen and the convenience of an STR. This includes adults with estimated creatinine clearance ≥ 30 mL/min who are initiating ARV treatment, or those virologically suppressed patients wishing to switch from an FTC/TDF-based STR such as Complera or Atripla for the aforementioned benefits. In addition, virologically suppressed patients receiving one of the NNRTIs such as EFV or RPV, in combination with FTC/TAF (Descovy) or other dual NRTI backbones, may benefit from the convenience of the STR

FTC/RPV/TAF. FTC/RPV/TAF is also the smallest STR approved by Health Canada and this may be useful for patients who have difficulty swallowing large pills.

1.3.3 Dosing Considerations

The Health Canada–recommended dose of FTC/RPV/TAF is one tablet once daily with food.[13] Thus, a single tablet of FTC/RPV/TAF is comparable to a multi-tablet regimen consisting of one tablet of Descovy (FTC/TAF 200/25 mg) plus one tablet of Edurant (RPV 25 mg). The Health Canada–recommended dosages for the separate products are consistent with the dosing of the STR. The Health Canada–recommended dose of Descovy 200/25 mg when used in combination with other non-PI antivirals is one tablet once daily with or without food[16]; for Edurant 25 mg when used in combination with other antivirals, it is one tablet once daily taken with a meal.[20] No dose titration is required for any of the aforementioned products.

2. CLINICAL EVIDENCE

At the time of the Health Canada submission, no efficacy or safety data were available for FTC/RPV/TAF in HIV-infected patients. Data submitted to Health Canada included the pivotal bioequivalence study (Study GS-US-366-1159)[22] comparing FTC/RPV/TAF to both Edurant (RPV 25 mg) and Genvoya (elvitegravir [EVG]/cobicistat [COBI]/FTC/TAF 150/150/200/10 mg); see Table 3. The methods and findings of the pivotal bioequivalence study of FTC/RPV/TAF are described in section 0.

TABLE 3: DETAILS FOR STUDY GS-US-366-1159

Study Name	Design	Objectives	Population
GS-US-366-1159[22]	Pivotal phase I randomized OL single-dose, three-way, six-sequence, crossover trial. N = 96	• To evaluate the bioequivalence of FTC and TAF administered as EVG/COBI/FTC/TAF (Genvoya) or as FTC/RPV/TAF • To evaluate the bioequivalence of RPV administered as Edurant (25 mg tablet) or as FTC/RPV/TAF	HIV-negative males and nonpregnant, nonlactating females aged 18 to 45 years, an eGFR ≥ 70 mL/min, and in good general health

COBI = cobicistat; eGFR = estimated glomerular filtration rate; EVG = elvitegravir; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; OL = open label; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate.

In addition, the Health Canada submission included supportive efficacy and safety data for the components of FTC/RPV/TAF based on phase II and phase III trials of Genvoya, Edurant, and the RPV-containing regimen Complera (FTC/RPV/TDF 200/25/300 mg); see section 0.

Subsequent to the Health Canada submission, interim data from two ongoing phase III studies of FTC/RPV/TAF (GS-US-366-1160 and GS-US-366-1216)[23-25] have become available. Interim findings of the ongoing phase III clinical trials of FTC/RPV/TAF are provided in section 0.

2.1 Pivotal Clinical Studies

2.1.1 Studies Submitted to Health Canada in Support of the Efficacy of FTC/RPV/TAF

The efficacy and safety of FTC/RPV/TAF in HIV-infected patients is supported by data from trials of Genvoya (EVG/COBI/FTC/TAF 150/150/200/10 mg), Edurant (RPV 25 mg tablet) when given with (FTC/TDF 200/300 mg), and Complera (FTC/RPV/TDF 200/25/300 mg). These supportive trials have established the safety and efficacy of the components of FTC/RPV/TAF in a broad population of patients infected with HIV-1, including treatment-naive adults, virologically suppressed adults, and adults with mild to moderate renal impairment; see Table 4.

TABLE 4: TRIALS SUBMITTED TO HEALTH CANADA IN SUPPORT OF THE EFFICACY AND SAFETY OF FTC/RPV/TAF

Study	Design	Main Inclusion Criteria	Treatments	Primary End Point
Genvoya (EVG/COBI/FTC/TAF) Studies				
HIV-infected, ART-Naive Adults				
GS-US-292-0104[26] Randomized: N = 872 Treated: N = 867 GS-US-292-0111[26] Randomized: N = 872 Treated: N = 866	Phase III multi-centre DB double-dummy active controlled RCT	• Adults (≥ 18 years) • Plasma HIV-1 RNA ≥ 1,000 copies/mL • No prior ART • HIV-1 genotype sensitive to EVG, FTC, and TFV • eGFR ≥ 50 mL/min	Genvoya: one tablet OD versus Stribild: one tablet OD Duration: 144 weeks	Primary: Percentage of participants with HIV RNA < 50 copies/mL at week 48
GS-US-292-0102[15] Randomized: N = 171 Treated: N = 170	Phase II multi-centre DB double-dummy active controlled RCT	• Adults (≥ 18 years) • Plasma HIV-1 RNA ≥ 5,000 copies/mL • CD4+ cell count > 50 cells/µL • No prior ART • HIV-1 genotype sensitive to FTC and TFV • eGFR ≥ 70 mL/min	Genvoya: one tablet OD versus Stribild: one tablet OD Duration: 48 weeks, with single-arm OL extension	Primary: Percentage of participants with HIV RNA < 50 copies/mL at week 24
HIV-Infected, Virologically Supressed Adults				
GS-US-292-0109[27] Randomized: N = 1443 Treated: N = 1436	Phase III multi-centre OL RCT switch study	• Adults (≥ 18 years) • Virologically supressed (HIV-1 RNA < 50 copies/mL) for ≥ 6 consecutive months prior to screening while receiving one of four specified FTC/TDF-containing regimens • eGFR ≥ 50 mL/min	Genvoya: one tablet OD versus Prior treatment regimen comprising TDF/FTC plus third agent Duration: 96 weeks	Primary: Percentage of participants with HIV RNA < 50 copies/mL at week 48
HIV-Infected Adults with Mild to Moderate Renal Failure				
GS-US-292-0112[28] Treated: N = 248	Phase III, non-randomized OL multi-centre, multi-cohort study	• Adult HIV-infected patients (aged ≥ 18 years) • CD4+ cell count ≥ 50 cells/µL • Stable eGFR 30 mL to 69 mL/min for three months prior to screening	Genvoya: one tablet OD Duration: 96 weeks	Primary: Assess changes in renal function at 24 weeks
Edurant (RPV) Studies				
HIV-Infected, ART-Naive Adults				
TMC278-C204[29] Randomized:	Phase IIb multinational partially blinded dose-finding	• Adults (≥ 18 years) • Plasma HIV-1 RNA >	Treatment groups: RPV 25 mg OD	Primary: Percentage of

Study	Design	Main Inclusion Criteria	Treatments	Primary End Point
N = 368 Treated: N = 368	RCT	5,000 copies/mL • No prior ART • Viral sensitivity to all concomitant NRTIs	RPV 75 mg OD RPV 150 mg OD EFV 600 mg OD All in combination with: FTC/TDF or AZT/3TC Duration: 96 weeks	participants with HIV RNA < 50 copies/mL at week 48
C209 (ECHO)[30,31] Randomized: N = 694 Treated: N = 690 C215 (THRIVE)[30,32] Randomized: N = 680 Treated: N = 678	Phase III multinational DB double-dummy active controlled RCT	• Adults (≥ 18 years) • Plasma HIV-1 RNA ≥ 5,000 copies/mL • No prior ART • Viral sensitivity to all study drugs (ECHO) or background NRTIs (THRIVE)	RPV 25 mg OD versus EFV 600 mg OD both given in combination with: FTC/TDF (ECHO), and with FTC/TDF, AZT/3TC or ABC/3TC (THRIVE) Duration: 96 weeks	Primary: Percentage of participants with HIV RNA < 50 copies/mL at week 48
Complera (FTC/RPV/TDF) Studies				
GS-US-264-0106 (SPIRIT)[33] Randomized: N = 482 Treated: N=476	Phase IIIb OL multi-centre RCT switch study	• Adults (> 18 years) • Virologically supressed (HIV-1 RNA < 50 copies/mL) for ≥ 6 months prior to screening while receiving a regimen of ritonavir-boosted PI plus two NRTIs. • Viral sensitivity to all study drugs	Weeks 0-24 Complera: one tablet OD versus Prior treatment regimen Weeks 24-48 All patients received Complera: one tablet OD Duration: 48 weeks	Primary: Percentage of participants with HIV RNA < 50 copies/mL at week 24
GS-US-264-0111[34] Treated: N = 49	Phase IIb OL multi-centre single-arm trial	Adults (≥ 18 years) receiving a first ARV regimen of EFV/FTC/TDF for ≥ 3 months with undetectable plasma HIV-1 RNA levels for ≥ 8 weeks prior to screening, who elected to switch regimens due to EFV intolerance and no resistance to study drugs	All patients received Complera: one tablet OD Duration: 48 weeks	Primary: Percentage of participants with HIV RNA < 50 copies/mL at Week 12

3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; AZT = zidovudine; COBI = cobicistat; DB = double blind; EFV = efavirenz; eGFR = estimated glomerular filtration rate; EVG = elvitegravir; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; N = number; NRTI = nucleos(t)ide reverse transcriptase inhibitor; OD = once daily; OL = open label; PI = protease inhibitor; RCT = randomized controlled trial; RNA = ribonucleic acid; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; TFV = tenofovir.
Note: STRs are Complera = FTC/RPV/TDF (200/25/300 mg); Genvoya = EVG/COBI/FTC/TAF (150/150/200/10 mg); and Stribild = EVG/COBI/FTC/TDF (150 /150/200/300 mg).

Trials of FTC/TAF- and RPV-containing regimens produced high rates of virologic success (primary end point: HIV RNA < 50 copies/mL) in all HIV-infected populations studied as described below.

a) ART-Naive Adults

In ART-naive adults, EVG/COBI/FTC/TAF (Genvoya) was noninferior to EVG/COBI/FTC/TDF (Stribild); virologic success at 48 weeks, 92% versus 90%, respectively, based on pooled analysis of studies GS-US-292-0104 and GS-US-292-0111.[26] Pooled 96-week data from studies GS-US-292-0104, and GS-US-292-0111 demonstrated that the FTC/TAF-containing regimen (Genvoya) produced a high rate of virologic success (87%) and remained noninferior to the FTC/TDF containing regimen (Stribild 85%).[35] In Study GS-US-292-0102, [redacted] of patients treated with the FTC/TAF-containing regimen, Genvoya, achieved virologic success at 96 weeks.[36] Finally, 144-week pooled data from studies GS-US-292-0104 and GS-US-292-0111 demonstrated that Genvoya was statistically superior to Stribild with virologic success reported in 84% and 80% of patients, respectively. In addition, RPV administered with FTC/TDF was noninferior to EFV plus FTC/TDF; virologic success at 48 weeks was 84% versus 82%, respectively, based on pooled analysis of ECHO and THRIVE studies.[30] Similarly, at 96 weeks, the proportion of patients with HIV-1 RNA < 50 copies/mL was comparable between the RPV and EFV treatment groups (76.9% and 77.3%, respectively) based on pooled analysis of ECHO and THRIVE.[13]

b) Virologically Suppressed Adults

In virologically suppressed adults switching from standard-of-care regimens, FTC/TAF- and RPV-containing regimens maintained efficacy compared with prior therapy. In Study GS-US-292-0109, EVG/COBI/FTC/TAF (Genvoya) was statistically superior to continuing on a regimen of FTC/TDF plus third agent; virologic success at week 48 was 97% versus 93%, respectively.[27] In Study GS-US-264-0106, switching to FTC/RPV/TDF (Complera) was noninferior to continuation of ritonavir-boosted PI plus two NRTIs; virologic success at week 24 was 93.7% versus 89.9%, respectively.[33]

c) Mild to Moderate Renal Impairment

In adults with mild to moderate renal impairment (Study GS-US-292-0112), patients who switched to EVG/COBI/FTC/TAF (Genvoya) maintained virologic success at week 48 (92%), supporting the use of an FTC/TAF-containing regimen in patients with estimated glomerular filtration rate (eGFR) of ≥ 30 mL/min without dose modification.[28] Approximately 65% of patients who switched to Genvoya in Study GS-US-292-0112 had received a TDF-containing regimen prior to enrolment, while 22% of patients switched from an ABC/3TC (lamivudine)-containing regimen.

Across all of the EVG/COBI/FTC/TAF and RPV studies, analyses of the secondary HIV-1 RNA end points supported the primary efficacy analyses. In addition, the immunologic benefit of treatment with FTC/TAF- and RPV-containing regimens was demonstrated by improvements in CD4 cell counts. Generally, there was no difference in efficacy across the different subpopulations evaluated, indicating that FTC/TAF- and RPV-containing regimens are efficacious in all populations without regard to demographic characteristics or underlying renal function. However, for RPV (Studies C209 and C215) the proportion of virologic responders at week 96 was greater in subjects with baseline viral load ≤ 100,000 copies/mL than in those with baseline viral load > 100,000 copies/mL.[13] Thus, FTC/RPV/TAF should not be used in patients with a baseline HIV-1 RNA > 100,000 copies/mL.[13]

Ongoing Phase III Trials of FTC/RPV/TAF

Study GS-US-366-1160 – Interim 48-Week Results

[redacted][23]

A. Study Characteristics

Study GS-US-366-1160 is a phase IIIb, randomized, double-blind, multi-centre study to evaluate the efficacy, safety, and tolerability of switching to FTC/RPV/TAF from EFV/TDF/FTC (Atripla) in virologically suppressed, HIV-infected patients (see Table 5). This study is ongoing. The data presented in this section assess the primary and secondary objectives through week 48, using a data cut-off when all randomized patients had completed the week-48 visit or had discontinued study drugs before their week-48 visit.

TABLE 5: DETAILS FOR STUDY GS-US-366-1160

Characteristics		Details for Study GS-US-366-1160
STUDY DESIGN	**Objective**	To evaluate the noninferiority of switching to FTC/RPV/TAF as compared to continuing Atripla in virologically suppressed HIV-infected patients
	Blinding	Double-blind
	Study period	Study start date: January 2015 This study is ongoing; the last subject observation for this report occurred July 2016
	Study centres	120 sites in eight countries including: 85 sites in the US, nine in Germany, eight in Canada, six in Spain, and four in the UK
	Design	RCT, noninferiority
STUDY POPULATION	**Randomized (N)**	881
	Inclusion criteria	HIV-infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of Atripla for ≥ 6 consecutive months prior to screening, with no documented resistance to any of the study agents at any time, and eGFR ≥ 50 mL/min
	Exclusion criteria	Hepatitis B or hepatitis C antibody-positive; decompensated cirrhosis; females who were breastfeeding or pregnant
DRUGS	**Intervention**	FTC/RPV/TAF 200/25/25 mg, one tablet, once daily
	Comparator(s)	Atripla (EFV/FTC/TDF 600/200/300 mg), one tablet once daily
DURATION	**Run-in**	NA
	Treatment	96 weeks
	Follow-up	Open-label FTC/RPV/TAF for up to an additional 48 weeks
OUTCOMES	**Primary end point(s)**	The percentage of patients with HIV-1 RNA < 50 copies/mL at week 48, as determined by the US FDA–defined snapshot algorithm
	Other end points	• Change from baseline in HIV symptoms index score • Percentage change from baseline in hip and spine BMD • Other safety assessments included adverse events, clinical laboratory tests, and measures of renal safety
NOTES	**Publications**	• None

BMD = bone mineral density; EFV = efavirenz; eGFR = estimated glomerular filtration rate; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; NNRTI = non-nucleoside reverse transcriptase inhibitor; RCT = randomized controlled trial; RNA = ribonucleic acid; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

Intervention and Comparators

Patients were randomized in a 1:1 ratio to one of the following two treatment groups:

- **Treatment group 1:** FTC/RPV/TAF 200/25/25 mg administered orally once daily plus placebo-to-match Atripla administered orally once daily
- **Treatment group 2:** Atripla (EFV/FTC/TDF 600/200/300 mg) administered orally once daily plus placebo-to-match FTC/RPV/TAF administered orally once daily

Patients were instructed to take the FTC/RPV/TAF tablet (or matching FTC/RPV/TAF placebo tablet) with food at the same time each day, and to take the Atripla tablet (or matching Atripla placebo tablet) at bedtime on an empty stomach. The use of medications for the treatment of HIV, other than the study treatment (i.e., FTC/RPV/TAF or Atripla), was prohibited.

Outcomes

The primary efficacy end point was the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48, as defined by the US FDA–defined snapshot algorithm. In this algorithm, patients whose last available HIV-1 RNA value in the week 48 analysis window (i.e., from weeks 42 through 54) was < 50 copies/mL were considered as having had a response; patients whose HIV-1 RNA level was ≥ 50 copies/mL in the analysis window, or who did not have available data in the analysis window, were considered as not having had a response.[37] Secondary efficacy outcomes (at week 48) included the proportion of patients with HIV-1 RNA < 20 copies/mL and the change from baseline in CD4 count.

Three key secondary (safety) end points were defined:

- Percentage change from baseline in hip and spine BMD at week 48
- Change from baseline in HIV symptoms index score at week 48

Additional safety assessments included AEs, physical examination, clinical laboratory tests and measures of renal safety.

Statistical Analyses

The primary efficacy end point was analyzed to assess the noninferiority of treatment with FTC/RPV/TAF relative to treatment with Atripla. Noninferiority was assessed using a conventional 95% confidence interval approach, with a noninferiority margin of 8%. It was concluded that FTC/RPV/TAF was noninferior to Atripla if the lower bound of the two-sided 95% confidence interval of the difference in the response rate (FTC/RPV/TAF − Atripla) was greater than −8%. If noninferiority was established, superiority of FTC/RPV/TAF over Atripla was evaluated.[23] The primary analysis used the full analysis set (FAS; all patients who received at least one dose of study drug). The week 48 per protocol (PP) analysis set (comprising those in the FAS who had not committed any major protocol violations) was also employed to evaluate the robustness of the primary analysis.

All safety data collected on or after the date of the first dose of study drug up to the last dose date of study drug plus 30 days for patients who permanently discontinued study drug, or all available data for patients who were still on study drug, were summarized for patients in the safety analysis set. Safety data were summarized by treatment group using descriptive statistics.[23]

The percentage changes from baseline in hip BMD and spine BMD at week 48 were summarized using descriptive statistics for patients in the hip and spine dual energy X-ray absorptiometry analysis sets, respectively, and compared between the two treatment groups at each visit using an analysis of variance (ANOVA) model, including treatment as a fixed effect. [redacted]

[redacted]

If noninferiority of the primary efficacy end point was established, multiplicity adjustments were planned for three key secondary end points at week 48 with a fallback procedure in the following sequential order with pre-specified two-sided alpha levels: hip BMD (alpha = 0.02); spine BMD (alpha = 0.02); [redacted].

B. Results

Baseline Characteristics

Demographic and disease characteristics were similar between the two treatment groups (Table 4). The study enrolled a virologically suppressed, HIV-infected population; therefore, 98.5% of patients in the safety analysis set had baseline HIV-1 RNA < 50 copies/mL.

TABLE 6: GS-US-366-1160: DEMOGRAPHIC AND DISEASE CHARACTERISTICS AT BASELINE (SAFETY ANALYSIS SET)

	FTC/RPV/TAF (N = 438)	Atripla (N = 437)	Total (N = 875)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Sex at Birth			
Male	373 (85.2%)	390 (89.2%)	763 (87.2%)
Race			
[redacted]	[redacted]	[redacted]	[redacted]
Asian	9 (2.1%)	8 (1.8%)	17 (1.9%)
Black	118 (26.9%)	120 (27.5%)	238 (27.2%)
[redacted]	[redacted]	[redacted]	[redacted]
White	291 (66.4%)	292 (66.8%)	583 (66.6%)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
HIV-1 RNA Categories (copies/mL)			
< 50	430 (98.2%)	432 (98.9%)	862 (98.5%)
≥ 50	8 (1.8%)	5 (1.1%)	13 (1.5%)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

	FTC/RPV/TAF (N = 438)	Atripla (N = 437)	Total (N = 875)
[redacted]	[redacted]	[redacted]	[redacted]

FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; N = number; RNA = ribonucleic acid; RPV = rilpivirine; SD = standard deviation; TAF = tenofovir alafenamide fumarate.

Patient Disposition

A total of 974 patients were screened and 881 patients were randomized. Of these, 875 patients received at least one dose of study drug and were included in the safety analysis set and FAS (FTC/RPV/TAF 438 patients; Atripla 437 patients). Of the 875 patients treated with study drug, [redacted] (78 patients) discontinued study drug treatment prior to the data cut-off date (FTC/RPV/TAF [redacted], 43 patients; Atripla [redacted], 35 patients), [redacted]. The most common reasons patients prematurely discontinued study drug are summarized in Table 5.

TABLE 7: SUMMARY OF PATIENT DISPOSITION FOR GS-US-366-1160 AT DATA CUT-OFF

Disposition	GS-US-366-1160	
	FTC/RPV/TAF	Atripla
Screened, N	974	
Randomized, N	440	441
Patients prematurely discontinuing study drug prior to the data cut-off date, N (%)	43 [redacted]	35 [redacted]
***WDAEs,* N (%)**	11 [redacted]	8 [redacted]
***Death,* N (%)**	1 [redacted]	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
***Protocol violation,* N (%)**	1 [redacted]	0
***Withdrew consent,* N (%)**	17 [redacted]	15 [redacted]
***Lost to follow-up,* N (%)**	5 [redacted]	6 [redacted]
Full analysis set, N	438	437
[redacted]	[redacted]	[redacted]
Safety, N	438	437

FTC = emtricitabine; N = number; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate; WDAE = withdrawal due to adverse event.

Efficacy

[redacted] Based on the primary analysis (see Table 8), switching to FTC/RPV/TAF was noninferior to maintaining Atripla; percentage of patients with virologic success at week 48 was 90.0% and 92.0%, respectively; treatment difference –2.0, 95% confidence interval, –5.9 to 1.8%. These results were confirmed in the PP analysis. In addition, the percentage of patients achieving HIV-1 RNA < 20 copies/mL at week 48 were 86.5% and 90.4% of patients treated with FTC/RPV/TAF and Atripla, respectively; treatment difference, –3.9%, 95% confidence interval, –8.2% to 0.5%.

TABLE 8: GS-US-366-1160: VIROLOGIC OUTCOME AT WEEK 48 USING THE US FDA–DEFINED SNAPSHOT ALGORITHM HIV-1 RNA < 50 COPIES/ML (FULL ANALYSIS SET)

	FTC/RPV/TAF (N = 438)	Atripla (N = 437)	FTC/RPV/TAF Versus Atripla	
			P Value	Difference in Percentages (95.001% CI)
HIV-1 RNA < 50 copies/mL	394 (90.0%)	402 (92.0%)	0.35	–2.0% (–5.9% to 1.8%)
HIV-1 RNA ≥ 50 copies/mL	5 (1.1%)	4 (0.9%)	1.00	0.2% (–1.4% to 1.8%)
No virologic data in week 48 window	39 (8.9%)	31 (7.1%)	NA	NA
HIV-1 RNA < 20 copies/mL	379 (86.5%)	395 (90.4%)	NR	–3.9% (–8.2% to 0.5%)

CI = confidence interval; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; N = number; NA = not applicable; NR = not reported; RNA = ribonucleic acid; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate.

[redacted]. CD4 cell counts were maintained in both treatment groups: mean (standard deviation [SD]) changes from baseline at week 48 (FAS, observed data) were as follows: FTC/RPV/TAF, 23 (156.4) cells/µL; Atripla, 12 (153.3) cells/µL ([redacted]).

Resistance development to FTC/RPV/TAF or Atripla was rare. The resistance analysis population (RAP) included any patient who received at least one dose of study drug, maintained their study drug regimen (or within 72 hours after interruption or discontinuation of study drugs), and exhibited either virologic rebound or any subject with HIV RNA ≥ 400 copies/mL at the final time point. The RAP comprised eight patients through week 48: six patients in the FTC/RPV/TAF group ([redacted]) and two patients in the Atripla group ([redacted]). Four patients in the FTC/RPV/TAF group [redacted] resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs. No patients from the FTC/RPV/TAF group developed resistance to study drugs. One patient in the Atripla group had emergent resistance to study drugs.

Results for the key safety end points ([redacted], hip BMD, and spine BMD) are presented in section 2.4.3.

Study GS-US-366-1216 Interim 48-Week Results

[redacted]

A. Study Characteristics

Study GS-US-366-1216 is an ongoing study similar in design to Study GS-US-366-1160, but evaluates the efficacy, safety, and tolerability of switching to FTC/RPV/TAF from FTC/RPV/TDF (Complera) in HIV-infected patients who have been virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of Complera for greater than or equal to six consecutive months at screening.

TABLE 9: DETAILS FOR STUDY GS-US-366-1216

Characteristics		Details for GS-US-366-1216
STUDY DESIGN	**Objective**	To evaluate the noninferiority of switching to FTC/RPV/TAF as compared to continuing Complera in virologically suppressed HIV-1 infected patients
	Blinding	Double-blind
	Study period	Study start date: January 2015 This study is ongoing; the last subject observation for this report occurred in July 2016
	Study centres	119 sites in 11 countries: 79 sites in the US, 10 in Germany, seven in Canada, seven in Spain, and six in the UK
	Design	RCT noninferiority
STUDY POPULATION	**Randomized (N)**	632
	Inclusion criteria	HIV-infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of Complera for ≥ 6 consecutive months prior to screening, with no documented resistance to any of the study agents, and who had an eGFR ≥ 50 mL/min
	Exclusion criteria	Hepatitis B or hepatitis C antibody-positive; decompensated cirrhosis; females who were breastfeeding or pregnant
DRUGS	**Intervention**	FTC/RPV/TAF 200/25/25 mg, one tablet once daily
	Comparator(s)	Complera (FTC/RPV/TDF 200/25/300 mg), one tablet once daily
DURATION	**Run-in**	NA
	Treatment	96 weeks
	Follow-up	Open-label FTC/RPV/TAF for up to an additional 48 weeks
OUTCOMES	**Primary end point(s)**	The proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 as defined by the US FDA–defined snapshot algorithm
	Other end points	• Percentage change from baseline in hip and spine BMD • Other safety assessments included adverse events, clinical laboratory tests, and measures of renal safety
NOTES	**Publications**	• None

BMD = bone mineral density; EFV = efavirenz; eGFR = estimated glomerular filtration rate; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; NA = not applicable; RCT = randomized controlled trial; RNA = ribonucleic acid; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

Intervention and Comparators

Patients were randomized in a 1:1 ratio to one of the following two treatment groups:

- **Treatment group 1:** FTC/RPV/TAF 200/25/25 mg administered orally once daily plus placebo-to-match Complera administered orally once daily with food at approximately the same time each day
- **Treatment group 2:** Complera (FTC/RPV/TDF 200/25/300 mg) administered orally once daily plus placebo-to-match FTC/RPV/TAF administered orally once daily with food at approximately the same time each day

The use of medications for the treatment of HIV, other than the study treatment (i.e., FTC/RPV/TAF or Complera), was prohibited.

Outcomes

Primary and secondary efficacy end points are identical to those described previously for Study GS-US-366-1160 except that there are only two key safety end points: the percentage changes from baseline in hip and spine BMD at week 48.

Please refer to the relevant sections for Study GS-US-366-1216 above [redacted].

Statistical Analyses

The statistics protocols are identical to those described previously for Study GS-US-366-1160 except that all analyses are relative to Complera. Please refer to the "statistical analyses" section for Study GS-US-366-1160 above [redacted]

B. Results

Baseline Characteristics

Demographic and general baseline characteristics were similar between the two treatment groups (see Table 8). The study enrolled a virologically suppressed, HIV-infected population; therefore, 98.3% of patients in the safety analysis set had baseline HIV-1 RNA < 50 copies/mL.

TABLE 10: GS-US-366-1216: DEMOGRAPHIC AND DISEASE CHARACTERISTICS AT BASELINE (SAFETY ANALYSIS SET)

	FTC/RPV/TAF (N = 316)	Complera (N = 314)	Total (N = 630)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Sex at Birth			
Male	275 (87.0%)	289 (92.0%)	564 (89.5%)
Female	41 (13.0%)	25 (8.0%)	66 (10.5%)
Race			
[redacted]	[redacted]	[redacted]	[redacted]
Asian	7 (2.2%)	17 (5.4%)	24 (3.8%)
Black	65 (20.6%)	54 (17.2%)	119 (18.9%)
[redacted]	[redacted]	[redacted]	[redacted]
White	238 (75.3%)	235 (74.8%)	473 (75.1%)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
HIV-1 RNA Categories (copies/mL)			
< 50	307 (97.2%)	312 (99.4%)	619 (98.3%)
≥ 50	9 (2.8%)	2 (0.6%)	11 (1.7%)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

	FTC/RPV/TAF (N = 316)	Complera (N = 314)	Total (N = 630)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; N = number; RNA = ribonucleic acid; RPV = rilpivirine; SD = standard deviation; TAF = tenofovir alafenamide fumarate.

Patient Disposition

A total of 690 patients were screened in this study, 632 of who were randomized, and 630 of who received at least one dose of study drug (FTC/RPV/TAF 316 patients; Complera 314 patients). Of the 630 patients treated with study drug, [redacted](36 patients) discontinued study drug treatment prior to the data cut-off date (FTC/RPV/TAF [redacted], 18 patients; Complera [redacted], 18 patients) [redacted]. The most common reasons patients prematurely discontinued the study drug are summarized in Table 11.

TABLE 11: SUMMARY OF PATIENT DISPOSITION FOR STUDY GS-US-366-1216 AT DATA CUT-OFF

Disposition	GS-US-366-1216	
	FTC/RPV/TAF	Complera
Screened, N	690	
Randomized, N	316	316
Discontinued, N (%)	18 ([redacted])	18 ([redacted])
WDAEs, N (%)	4 ([redacted])	3 ([redacted])
Death, N (%)	1 ([redacted])	1 ([redacted])
Pregnancy, N (%)	1 ([redacted])	0
Lack of efficacy, N (%)	0	0
Investigator's discretion, N (%)	2 ([redacted])	2 ([redacted])
Non-compliance with study drug, N (%)	0	1 ([redacted])
Protocol violation, N (%)	2 ([redacted])	0
Withdrew consent, N (%)	6 ([redacted])	8 ([redacted])
Lost to follow-up, N (%)	2 ([redacted])	3 ([redacted])
Full analysis set, N	316	313
[redacted]	[redacted]	[redacted]
Safety, N	316	314

FTC = emtricitabine; N = number; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate; WDAE = withdrawal due to adverse event.

Efficacy

[redacted] Based on the primary analysis (see Table 12), switching to FTC/RPV/TAF was noninferior to maintaining Complera. The percentage of patients with virologic success at week 48 was 93.7% and 93.9%, respectively; treatment difference −0.3%, 95% confidence interval, –4.2% to 3.7%. These results were confirmed in the PP analysis. In addition, the percentage of patients achieving HIV-1 RNA < 20 copies/mL at week 48 were 91.8% and 90.4% of patients treated with

FTC/RPV/TAF and Complera, respectively; treatment difference 1.4%, 95% confidence interval, –3.2% to 6.0%.

TABLE 12: GS-US-366-1216: VIROLOGIC OUTCOME AT WEEK 48 USING THE US FDA–DEFINED SNAPSHOT ALGORITHM AND HIV-1 RNA < 50 COPIES/ML (FULL ANALYSIS SET)

	FTC/RPV/TAF (N = 316)	Complera (N = 313)	FTC/RPV/TAF Versus Complera	
			P Value	Difference in Percentages (95.001% CI)
HIV-1 RNA < 50 copies/mL	296 (93.7%)	294 (93.9%)	1.00	−0.3% (−4.2% to 3.7%)
HIV-1 RNA ≥ 50 copies/mL	2 (0.6%)	0	0.50	0.6% (−0.6% to 2.3%)
No virologic data in week 48 window	18 (5.7%)	19 (6.1%)		
HIV-1 RNA < 20 copies/mL	290 (91.8%)	283 (90.4%)	NR	1.4% (–3.2% to 6.0%)

CI = confidence interval; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; N = number; NA = not applicable; NR = not reported; RNA = ribonucleic acid; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate.

[redacted]. CD4 cell counts were maintained in both groups; mean (SD) changes from baseline at week 48 (FAS, observed data) were as follows: FTC/RPV/TAF 9 (159.7) cells/µL; Complera −1 (152.7) cells/µL ([redacted]).

There was no resistance development to FTC/RPV/TAF or Complera. The RAP comprised two patients through week 48 including one patient in the FTC/RPV/TAF group ([redacted]) and one patient in the Complera group ([redacted]). The patient in the Complera group resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs. The patient in the FTC/RPV/TAF group had re-emergence of archived resistance (M41L, E44D, D67N, V118I, L210W, and T215Y) and did not resuppress HIV-1 RNA to < 50 copies/mL.

Results of the key safety end points (hip and spine BMD) are presented in section 2.4.3.

2.2 Critical Appraisal of Pivotal Clinical Studies

The supportive studies submitted to Health Canada for the review of FTC/RPV/TAF were from the clinical development programs, included phase II and phase III trials of Genvoya, Edurant, and Complera.[8-10] All three of these drugs have been previously review by CADTH through the CDR process and received recommendations from CDEC to list or list with a condition.[9-11] Therefore, a critical appraisal of those studies is not included in this report, which focuses on the two studies that investigated the use of FTC/RPV/TAF (i.e., Study 1160 and Study 1216).

2.2.1 Internal Validity

Randomization in studies 1160 and 1216 was conducted using appropriate methods with adequate measures to conceal treatment allocation (i.e., interactive web response system [IWRS]).[12,13] Although randomization was not stratified according to any patient characteristics, the demographic and baseline characteristics were balanced between the FTC/RPV/TAF and comparator groups in both Study 1160 and Study 1216.[12,13] Compared with FTC/RPV/TAF, there were a greater proportion of males in the FTC/RPV/TDF group of Study 1216 (92.0% versus 87.0%) and in the EFV/FTC/TDF group of Study 1160 (89.2% versus 85.2%).

The primary end point of studies 1160 and 1216 was in accordance with FDA guidance (i.e., virologic success at 48 weeks). The noninferiority margin for the primary end point in both studies was 8% which is more conservative than some of the noninferiority margins that have been previously used in HIV clinical trials (range: 10% to 12.5%),[22] including those that were used in the phase III studies for Genvoya.[23] Although the use of a per-protocol (PP) analysis is typically considered to be a more conservative approach for the primary analysis in a noninferiority trial, the primary analysis in both studies 1160 and 1216 was conducted using the full analysis set (FAS) with a PP analysis used to investigate the robustness of the results.[12,13] The results were similar between the FAS and PP analysis in both Study 1160 and Study 1216;[12,13] therefore, the use of the FAS population in the primary analysis does not alter the interpretation of the results.

In both studies, nearly all of the randomized patients were included in the FAS data sets (875/881 [99.3%] in Study 1160 and 629/632 [99.5%] in Study 1216).[12,13] Withdrawals were infrequent with less than 10% of patients discontinuing from either study ([redacted]).[12,13] The proportion of patients who discontinued from the studies was similar between the FTC/RPV/TAF and EFV/FTC/TDF groups in Study 1160 ([redacted]) and between FTC/RPV/TAF and FTC/RPV/TDF in Study 1216 ([redacted]).[12,13] Across both studies the reasons for discontinuation were similar in the FTC/RPV/TAF and comparator groups.

Both studies included statistical testing hierarchies to control the type I error rate for the primary noninferiority analysis and the analyses of the key secondary endpoints of hip and spine BMD (both studies) and HIV symptoms index score (Study 1160).[12,13] Both studies featured an appropriate approach to analyze safety data, including adjusting for multiple statistical testing by using a fallback procedure. The studies used an ANOVA model, which included treatment as a fixed-effect, to compare the percentage change from baseline in hip BMD and spine BMD between the treatment groups. [redacted].

2.2.2 External Validity

Most of the trial patients were recruited from US centres, with eight and seven Canadian sites included in Studies 1160 and 1216, respectively. Patients with hepatitis B or hepatitis C co-infection were excluded from Studies 1160 and 1216.[12,13] Overall, the clinical expert consulted by CADTH indicated that the study populations were a reasonable reflection of those encountered in routine clinical practice.

Patients enrolled in studies 1160 and 1216 were required to have been on a stable regimen of Atripla or Complera for at least six consecutive months prior to screening. The clinical expert consulted by CADTH suggested that intolerance to Atripla or Complera would typically occur shortly after initiating treatment; therefore, the study population was enriched with those who were able to tolerate Atripla or Complera. Hence, the adverse events reported for the Atripla and Complera groups are a reflection of patients continuing on their existing treatment; whereas, those reported for the FTC/RPV/TAF groups are a reflection of patients initiating treatment with a new therapeutic regimen.

In Study 1160 and Study 1216, the dosage, timing, and route of administration for the active-treatments were in accordance with recommendations in the Canadian product monographs for FTC/RPV/TAF, Atripla, and Complera.[2,14,15] All of the treatments were administered in a double-blind manner using a double-dummy design. Therefore, the study regimens required patients to receive twice daily dosing rather than once daily dosing, which may have had a negative impact on patient adherence. However adherence to the study drugs was high in both Study 1160 ([redacted]) and Study 1216 ([redacted]). The clinical expert consulted by CADTH indicated that there is a high level of adherence to HIV treatment in clinical practice.

The manufacturer's requested listing criteria is for use of FTC/RPV/TAF as a complete regimen for the treatment of treatment-naive and virologically suppressed adults infected with HIV-1. Studies 1160 and 1216, the only RCTs conducted using the FTC/RPV/TAF formulation, were conducted exclusively in patients who were virologically suppressed (i.e., HIV 1 RNA < 50 copies/mL) on a stable regimen of Atripla (1160) or Complera (1216) for at least six months prior to screening.[12,13]

To be eligible for studies 1160 and 1216, patients were required to have an eGFR of at least 50 mL/min.[12,13] This is consistent with recommendations in the product monographs for Complera and Atripla;[14,15] however, the product monograph for FTC/RPV/TAF states that treatment should not be initiated in patients with eGFR less than 30 mL/min (i.e., a lower threshold).[2] The manufacturer reported that the eGFR threshold set for studies 1160 and 1216 was required to be ≥ 50 mL/min in order to satisfy the requirements of the comparator groups (i.e., Atripla and Complera).[24]

2.3 Summary of Safety

2.3.1 Safety Evaluation Plan

At the time of the Health Canada submission, no efficacy or safety data were available from clinical trials of FTC/RPV/TAF in HIV-infected patients. Rather, the safety of FTC/RPV/TAF in a broad HIV-infected population was supported by previously described clinical trials of FTC/TAF- and RPV-containing regimens (see section 0), using a pharmacokinetic (PK) bioequivalence bridge between FTC/RPV/TAF and Genvoya (for the FTC/TAF component) and between FTC/RPV/TAF and Edurant (for the RPV component). Safety data from the supportive trials were submitted to Health Canada and are summarized below. [redacted] In addition, interim 48-week safety data from two ongoing phase III trials of FTC/RPV/TAF (GS-US-366-1160 and GS-US-366-1216) are provided below.

2.3.2 Safety Populations Evaluated

a) Supportive Trials (of FTC/TAF and RPV-Containing Regimens)

In phase II and III studies of Genvoya providing supportive safety evidence, 2,394 participants received at least one dose of Genvoya; 2,121 in phase III trials and 273 in the phase II trial (including the randomized phase and open-label extension). In the RPV studies providing supportive safety evidence, [redacted] patients received at least one dose of RPV 25 mg, including [redacted] participants in the RPV phase III studies and [redacted] patients in the RPV phase II study. In studies of Complera, a total of [redacted] patients received at least one dose of Complera; [redacted] patients in the phase III study, and [redacted] patients in the phase IIb study.

b) Ongoing Phase III Trials of FTC/RPV/TAF

In Study GS-US-366-1160, all 875 patients who were randomized and received study drug were included in the safety analysis set (FTC/RPV/TAF 438 patients; Atripla 437 patients). In Study GS-US-366-1216, of the 632 patients that were randomized, 630 patients received at least one dose of study drug and were included in the safety analysis set (FTC/RPV/TAF 316 patients; Complera 314 patients).

2.3.3 Overview of Safety

a) Supportive Safety Evidence from Trials of FTC/TAF and RPV-Containing Regimens

[redacted].

b) FTC/TAF-Containing Regimens (Genvoya Studies)

In Genvoya clinical trials, the AE profile was similar across a number of HIV-infected populations: ART-naive adults, virologically suppressed adults, and adults with mild to moderate renal impairment. AEs were frequently observed in all trials with a similar percentage of participants reporting any AE between treatment groups. The most commonly reported AEs among Genvoya-treated patients in studies GS-US-292-0104 and GS-US-292-0111 (pooled) were diarrhea (17.0%), nausea (15.2%), headache (14.3%), and upper respiratory infection (11.4%). Across all trials, AEs leading to study drug discontinuations were uncommon, ranging from [redacted] of Genvoya-treated patients. Four deaths were reported among those treated with Genvoya; two ART-naive adults (embolic stroke and alcohol poisoning) and two virologically suppressed adults (septic shock and adenocarcinoma). None of the events leading to death were considered drug-related. There were no deaths in the renally impaired population of Study GS-US-292-0112. Genvoya demonstrated an improved bone safety profile compared with Stribild or other TDF-containing regimens — specifically, lesser reductions in BMD at both the hip and spine for treatment-naive adults, and improvements in BMD for virologically suppressed adults (including those with renal impairment) who switched to Genvoya from a TDF-containing regimen.

In treatment-naive adults, mean percentage decreases from baseline in BMD at the hip or spine were smaller in the Genvoya group compared with the Stribild group ($P < 0.001$ for the differences between the two groups at week 24 and week 48). Mean (SD) hip BMD decreases from baseline at week 48 were as follows: Genvoya 0.657% (3.2646%) and Stribild 2.948% (3.4095%). Mean (SD) baseline spine decreases from baseline at week 48 were as follows: Genvoya 1.301% (3.0823%) and Stribild 2.862% (3.2460%). In studies GS-US-292-0104 and GS-US-292-0111, at week 144 there were no discontinuations due to renal AEs and no cases of renal tubulopathy or Fanconi syndrome among Genvoya-treated patients, compared with 12 of 867 Stribild-treated patients that discontinued due to renal AEs, including renal tubular disorder (n = 3), renal failure (n = 2) and Fanconi syndrome (n = 1). At week 144, there were no treatment discontinuations due to bone AEs among Genvoya-treated patients, compared with six of 867 Stribild-treated patients who discontinued due to decreased bone density (n = 3), bone loss (n = 1), osteopenia (n = 1), and osteoporosis (n = 1). The totality of the evidence from the Genvoya clinical trial program demonstrated that Genvoya is associated with an improved renal safety profile compared with Stribild or with other TDF-containing regimens based on a number of tests of renal function, including serum creatinine, eGFR, and proteinuria. No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported among patients receiving Genvoya. The safety profile of Genvoya in HIV-infected patients with mild to moderate renal impairment was similar to that in patients with normal renal function.

c) RPV-Containing Regimens (RPV and Complera Studies)

In the ECHO and THRIVE trials, the proportion of patients reporting any AE was similar between RPV and EFV groups. In pooled analysis, the proportion of patients experiencing an AE leading to permanent discontinuation was lower in the RPV group (3.8%) compared with the EFV group (8.6%) in the subset receiving the FTC/TDF backbone, similar to the overall study population. Compared with EFV, patients treated with RPV had a lower incidence of the following events of interest: skin (20.4% versus 31.5%), neurologic (27.8% versus 46.3%), psychiatric (28.9% versus 35.0%), and potentially QTc prolongation-related (0.5% versus 1.6%). Seven patients died in the phase III trials (ECHO and THRIVE), one in the RPV group in THRIVE, and six in the control groups (three in ECHO and three in THRIVE); none were considered drug-related. In studies of Complera, no new AEs were identified in virologically suppressed patients switching to Complera from a ritonavir-boosted PI, or from Atripla. Analyses from pooled BMD data from the ECHO and THRIVE trials showed that both treatment groups experienced a small but statistically significant median decrease from baseline in BMD (1.4% and 1.5% in the RPV group and 1.4% and 1.5% in the control group at weeks 48 and 96, respectively); between-group differences were not statistically significant. RPV groups in ECHO and THRIVE experienced mean increases from baseline in serum creatinine, most of which occurred within the first four weeks of treatment. Similarly, in the SPIRIT study, patients who switched to Complera demonstrated serum creatinine elevations, evident by week 4, that were statistically significantly higher compared with patients maintained on a ritonavir-boosted PI at week 24; 0.05 versus 0.01 mg/dL, respectively ($P < 0.001$). Due to the known inhibition of tubular secretion of creatinine by RPV, which has no effect on actual glomerular filtration, these changes were not considered clinically relevant.

d) Safety Evidence from Ongoing Phase III Trials of FTC/RPV/TAF

Study GS-US-366-1160

In patients switching to FTC/RPV/TAF from Atripla, FTC/RPV/TAF was generally well tolerated through a median of 47.9 weeks of exposure, as evidenced by the low rate of discontinuations due to AEs (2.5%) and the absence of study drug-related serious AEs. In patients who continued on Atripla, study drugs were generally well tolerated through a median of 48.0 weeks of exposure. Common AEs in both treatment groups were consistent with those expected in the study population. Statistically significant differences favouring FTC/RPV/TAF over Atripla at week 48 were observed for the first and second key safety end points (percentage changes from baseline in hip and spine BMD, respectively). Mean (SD) percentage changes from baseline to week 48 in hip BMD were 1.279% (2.3800%) for patients who switched to FTC/RPV/TAF and –0.134% (2.4930%) for patients who remained on Atripla; mean (SD) percentage changes from baseline to week 48 in spine BMD were 1.645% (3.3198%) and –0.045% (2.9087%) for FTC/RPV/TAF and Atripla, respectively ($P < 0.001$ for the differences in least squares means for FTC/RPV/TAF versus Atripla for both hip and spine).

[redacted].

There were differences between the two treatment groups in the renal laboratory parameters serum creatinine and eGFR. For patients who switched to FTC/RPV/TAF, there was an increase in serum creatinine and a decrease in eGFR was observed at week 4, which stabilized from week 12 through

week 48. The difference between treatment groups in change from baseline for serum creatinine and eGFR was statistically significant at all time points from week 4 through week 48 ($P < 0.001$ at all time points from week 4 through week 48 for both parameters). The increase in serum creatinine and decrease in eGFR in the FTC/RPV/TAF group is consistent with the known effects of RPV on tubular secretion of creatinine. Compared with Atripla, patients switched to FTC/RPV/TAF demonstrated statistically significant improvements (decreases) in proteinuria, albuminuria, and tubular proteinuria. No subject in either treatment group had proximal renal tubulopathy.

Study GS-US-366-1216

In patients switching to FTC/RPV/TAF from Complera, FTC/RPV/TAF was generally well tolerated through a median of 47.9 weeks of exposure, as evidenced by the infrequent discontinuations due to AEs (1.3%) and the absence of study drug–related serious AEs. In patients who continued on Complera, study drugs were generally well tolerated through a median of 48.0 weeks of exposure. Common AEs in both treatment groups were consistent with those expected in the study population.

Statistically significant differences favouring FTC/RPV/TAF over Complera at week 48 were observed for both of the key safety end points (percentage changes from baseline in hip and spine BMD). There were increases from baseline in mean (SD) BMD at the hip and spine in patients who switched to FTC/RPV/TAF, compared with minimal changes in both for patients who remained on Complera. Mean (SD) percentage changes at week 48 for hip were: FTC/RPV/TAF 1.040% (1.9404%) and Complera –0.245% (2.0805%). Mean (SD) percentage changes at week 48 for spine were: FTC/RPV/TAF 1.613% (3.4346%) and Complera 0.075% (2.9605%). ($P < 0.001$ for the difference between groups for both hip and spine.) Comparison of the changes from baseline in eGFR also favoured FTC/RPV/TAF over Complera, with statistically significant differences between treatment groups for the median change from baseline at all time points from week 8 through week 48 ($P = 0.002$ at week 48). Compared with Complera, patients switched to FTC/RPV/TAF demonstrated statistically significant improvements (decreases) in proteinuria, albuminuria, and tubular proteinuria. No subject in either treatment group had proximal renal tubulopathy.

2.4 Bioequivalence

The pivotal bioequivalence study for FTC/RPV/TAF, Study GS-US-366-1159,[22] was a randomized single-dose, open-label, three-way, six-sequence crossover phase I study that enrolled 96 healthy HIV-negative adults 18 to 45 years of age with a creatinine clearance ≥ 70 mL/min. The objective of the study was to evaluate the bioequivalence of FTC and TAF administered as FTC/RPV/TAF compared with Genvoya, and to evaluate the bioequivalence of RPV administered as FTC/RPV/TAF compared with Edurant. Genvoya was selected as a reference because the pivotal clinical data establishing the safety and efficacy of TAF in combination with FTC were generated using Genvoya in phase III studies. Edurant was selected as a reference because the safety and efficacy of RPV have been established from the Edurant phase III registrational studies. Patients were randomized to all three treatments (A, B, and C) in one of six treatment sequences (ABC, ACB, BAC, BCA, CAB, and CBA), with each single dose treatment to be administered over three treatment periods under fed conditions. Periods 1 and 2 were followed by a 14-day washout period. The three treatments are as described below:

- Treatment A (test product): FTC 200 mg, RPV 25mg, and TAF 25 mg as FTC/RPV/TAF
- Treatment B (reference product): RPV 25 mg as Edurant
- Treatment C (reference product): EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg as Genvoya.

The primary end points were the PK parameters, area under the plasma concentration versus time curve, both from time zero to the last quantifiable concentration (AUC_{last}) and extrapolated to infinity (AUC_{inf}), and the maximum plasma concentration (C_{max}). PK parameters were estimated using standard of noncompartmental methods from the plasma concentration-time data of the three treatments. The PK analysis sets for FTC, RPV, and TAF included all randomized patients who received at least one dose of study drug and had a least one plasma concentration point for the analyte. Bioequivalence of the test to reference treatments was concluded if the 90% confidence interval of the geometric least squares mean ratio of the PK parameters for each analyte was within 80% and 125%.

A total of 96 participants were randomized and received at least one dose of study drug. The PK analysis sets for FTC and TAF included all 96 participants, while 95 participants were included in the RPV analysis set. Plasma PK parameters for FTC, RPV, and TAF after administration of the test or reference treatment are provided in Table 13 FTC and TAF administered as FTC/RPV/TAF met the primary end points of the study and demonstrated bioequivalence to Genvoya under fed conditions. Similarly, RPV administered as the FTC/RPV/TAF demonstrated bioequivalence to Edurant. The 90% confidence intervals for the geometric least squares mean ratios of the AUC_{last}, AUC_{inf}, and C_{max} for test versus reference treatments were within 80% to 125% for FTC, RPV, and TAF, thus meeting Health Canada's criteria for establishing bioequivalence.[38]

TABLE 13: BIOEQUIVALENCE PROFILE FOR RILPIVIRINE/EMTRICITABINE/TENOFOVIR ALAFENAMIDE FUMARATE

Parameter	FTC as RPV/FTC/TAF	FTC as Genvoya	RPV as RPV/FTC/TAF	RPV as Edurant	TAF as RPV/FTC/TAF	TAF as Genvoya
AUC_{last}						
• Mean	9381.9	10159.4	3698.6	3373.4	250.0	238.4
• SD	NR	NR	NR	NR	NR	NR
• CV	21.7	21.5	34.9	40.0	43.4	36.5
• GLSM ratio	92.2	ref	111.7	ref	102.9	ref
• 90% CI	(90.8, 93.7)	ref	(106.3, 117.4)	ref	(98.2, 107.8)	ref
AUC_{inf}						
• Mean	9603.2	10387.1	3843.1	3540.7	263.6	247.4
• SD	NR	NR	NR	NR	NR	NR
• CV	21.6	21.5	36.2	43.0	42.0	36.1
• GLSM ratio	92.4	ref	110.5	ref	103.9	ref
• 90% CI	(90.9, 93.8)	ref	(105.8, 115.4)	ref	(98.3, 109.7)	ref
C_{max}						
• Mean	1608.6	1583.8	121.4	108.0	198.0	191.5
• SD	NR	NR	NR	NR	NR	NR
• CV	26.5	23.8	26.1	28.7	57.7	48.2
• GLSM ratio	100.8	ref	113.5	ref	100.8	ref
• 90% CI	97.5, 104.2	ref	108.4, 118.9	ref	91.6, 110.9	ref
T_{max}						
• Median	2.00	2.00	4.00	4.00	1.50	1.50
• 1^{st}, 3^{rd} quartile	1.50, 3.00	2.00, 3.00	4.00, 5.00	4.00, 5.00	1.00, 2.00	1.00, 2.00
• CV	NR	NR	NR	NR	NR	NR

AUC_{last} = area under the curve from time zero to last quantifiable concentration; AUC_{inf} = area under the curve extrapolated to infinity; CV = coefficient of variation; FTC = emtricitabine; GLSM = geometric least squares mean; NR = not reported; ref = reference; RPV = rilpivirine; SD = standard deviation; TAF = tenofovir alafenamide fumarate.
Source: Zack et al.[22]

3. PHARMACOECONOMIC EVALUATION

3.1 Manufacturer-Submitted Cost Information

TABLE 14: COST COMPARISON OF NEW COMBINATION PRODUCT AND INDIVIDUAL COMPONENTS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)
Emtricitabine/rilpivirine/ tenofovir alafenamide fumarate (brand name TBD)	Emtricitabine 200 mg Rilpivirine 25 mg Tenofovir alafenamide fumarate 25 mg	Tablet	$42.3670	One tablet daily	**$42.3670**
Rilpivirine (Edurant)	25 mg	Tablet	$15.0155	One tablet daily	$15.0155
Emtricitabine/tenofovir alafenamide fumarate (Descovy)	Emtricitabine 200 mg Tenofovir alafenamide fumarate 25 mg	Tablet	$28.5700	One tablet daily	$28.5700
Total					**$43.5855**

TBD = to be determined.
Note: Prices sourced from Ontario Drug Benefit e-Formulary, accessed October 31, 2016.

The combination product FTC/RPV/TAF at a list price of $42.3670/tablet/day saves $1.2185/day versus the individual components. Exclusive of markup, this is a savings of $444.75 per year in Ontario. Prices may differ by province.

No prices are confidential.

No patent expiry is directly applicable to the individual components Edurant and Descovy. Related products are subject to patent expiry as indicated in section 3.2.

Cost Comparison Table

RPV in combination with FTC and either formulation of tenofovir is listed as an alternative regimen in the US DHHS guidelines. These guidelines are widely used as the gold standard reference for appropriate ARV care, and CDR recommendations routinely refer to them. Table 15 lists all alternative regimens for the initial treatment of HIV infection.

Note: Atazanavir/COBI (Evotaz) is also an alternative regimen when combined with FTC/TAF or FTC/TDF; however, Evotaz is not commercially available in Canada and is therefore excluded from Table 15.

TABLE 15: COST COMPARISON TABLE

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
ATV/r + FTC/TAF	ATV 300 mg r 100 mg FTC 200 mg TAF 10 mg	Capsule + two tablets	Reyataz ($22.71) + Norvir ($1.52) + Descovy ($28.57)	Once daily	$52.80
ATV/r + FTC/TDF	ATV 300 mg r 100 mg FTC 200 mg TDF 300 mg	Capsule + two tablets	Reyataz ($22.71) + Norvir ($1.52) + Truvada ($29.08)	Once daily	$53.31
DRV/c + ABC/3TC	DRV 800 mg c 150 mg ABC 600 mg 3TC 300 mg	Two tablets	Prezcobix ($23.87) + ABC/3TC ($5.99)	Once daily	$29.85
DRV/c + FTC/TAF	DRV 800 mg c 150 mg FTC 200 mg TAF 10 mg	Two tablets	Prezcobix ($23.87) + Descovy ($28.57)	Once daily	$52.44
DRV/c + FTC/TDF	DRV 800 mg c 150 mg FTC 200 mg TDF 300 mg	Two tablets	Prezcobix ($23.87) + Truvada ($29.08)	Once daily	$52.95
DRV/r + ABC/3TC	DRV 800 mg r 100 mg ABC 600 mg 3TC 300 mg	Three tablets	Prezista ($21.72) + Norvir ($1.52) + ABC/3TC ($5.99)	Once daily	$29.22
EFV + FTC/TAF	EFV 600 mg FTC 200 mg TAF 25 mg	Two tablets	EFV ($3.80) + Descovy ($28.57)	Once daily	$32.37
EFV/FTC/TDF	EFV 600 mg FTC 200 mg TDF 300 mg	Single tablet	Atripla ($44.56)	Once daily	$44.56
FTC/RPV/TAF	**FTC 200 mg RPV 25 mg TAF 25 mg**	**Single tablet**	**FTC/RPV/TAF ($42.37)**	**Once daily**	**$42.37**
FTC/RPV/TDF	FTC 200 mg RPV 25 mg TDF 300 mg	Single tablet	Complera ($44.11)	Once daily	$44.11

3TC = lamivudine; ABC = abacavir; ATV = atazanavir (Reyataz); c = cobicistat; DRV = darunavir (Prezista); EFV = efavirenz (available as generic); FTC = emtricitabine; r = ritonavir (Norvir); RPV = rilpivirine (Edurant); TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.
Note: Combination products are ABC/3TC (available as generic); DRV/c (Prezcobix); EFV/FTC/TDF (Atripla); FTC/TAF (Descovy); FTC/TDF (Truvada); and FTC/RPV/TDF (Complera).
Source for prices: Ontario Drug Benefit e-Formulary, accessed October 31, 2016.
Source for dosage: DHHS Guidelines, downloaded October 31, 2016.

3.2 Manufacturer-Submitted Information Regarding Current Patent Status

TABLE 16: MANUFACTURER-SUBMITTED INFORMATION REGARDING CURRENT PATENT STATUS

Brand Name	Medicinal Ingredients and Strengths	DIN	Patent Number	Date of Expiry
TBD	200 mg emtricitabine, 25 mg rilpivirine, 25 mg tenofovir alafenamide fumarate	TBD	2,398,887	February 26, 2021
TBD	200 mg emtricitabine, 25 mg rilpivirine, 25 mg tenofovir alafenamide fumarate	TBD	2,416,757	July 20, 2021
TBD	200 mg emtricitabine, 25 mg rilpivirine, 25 mg tenofovir alafenamide fumarate	TBD	2,452,217	August 9, 2022
TBD	200 mg emtricitabine, 25 mg rilpivirine, 25 mg tenofovir alafenamide fumarate	TBD	2,537,095	September 3, 2024
TBD	200 mg emtricitabine, 25 mg rilpivirine, 25 mg tenofovir alafenamide fumarate	TBD	2,577,288	September 2, 2025

DIN = drug identification number; TBD = to be determined.

3.3 Critical Appraisal of Cost Information

The manufacturer conducted a cost comparison analysis of FTC/RPV/TAF single tablet regimen (STR) compared with other antiretroviral regimens for treatment-naive or virologically suppressed adults infected with HIV-1 (as per indication). At the submitted daily price of $42.37 per tablet (Table 14), the manufacturer noted that FTC/RPV/TAF is cost-saving (approximately $1 daily) compared with the sum of the costs of its individual components: RPV ($15.02 daily) and FTC/TAF ($28.57 daily). The Ontario Drug Benefit Formulary list price of RPV has increased marginally since the manufacturer's submission ($15.1370 daily),[25] increasing the cost savings of FTC/RPV/TAF to $1.34 per day (or $489.10 per year) compared with RPV + FTC/TAF. Should the cost of either individual component be lower in any jurisdiction than what was presented in the manufacturer's analysis, the cost savings of FTC/RPV/TAF may not be realized.

Given that FTC/RPV/TAF is currently recommended as an alternative regimen for the initial treatment of HIV infection in the 2016 DHHS guidelines,[1] the manufacturer compared the daily cost of FTC/RPV/TAF with other DHHS alternative antiretroviral regimens (
Table 15). The submitted daily price of FTC/RPV/TAF is lower than the current list price of its TDF-containing counterpart, FTC/RPV/TDF ($44.11 daily) and other alternative regimens, with the exception of ABC/3TC administered with either darunavir/cobicistat ($29.85 daily) or with darunavir/ritonavir ($29.22 daily) and efavirenz administered with FTC/TAF ($32.37 daily).

Feedback from the clinical expert consulted by CADTH for this review referred to DHHS-recommended and alternative regimens as treatment options but noted that most patients favour STRs over multi-tablet regimens owing to their convenient administration. As a result, CDR considered the costs of all DHHS-recommended and alternative regimens, including the five available STRs (Table 17). CDR noted that FTC/RPV/TAF was less costly than other DHHS-recommended regimens.
While the availability of FTC/RPV/TAF has the potential to displace the market share from other STR products, feedback from the clinical expert suggested that FTC/RPV/TAF is unlikely to be favoured over

other DHHS-recommended regimens but most likely to displace FTC/RPV/TDF. Utilization data from QuintilesIMS/Pharmastat (accessed: January 2017) regarding the use of STRs in Canada from 2012 to 2016 indicate that the uptake of DTG/ABC/3TC has markedly increased since its availability on Canadian public drug plans, surpassing that of other STR therapeutic options in 2016. Conversely, utilization of FTC/RPV/TDF has gradually decreased during the observed five-year period.[26] As such, the cost saving from FTC/RPV/TAF may be limited given the current use of FTC/RPV/TDF.

CDR also noted that while the availability of regimens in co-formulated fixed-dose combinations may be preferred by most patients due to their convenient dosing and administration, which may in turn improve adherence, these fixed-dose regimens present a challenge to generic entrants as individual drug patents expire. The patent for TDF is set to expire in 2018; however, savings which could result from the potential generic substitution of its brand name product will not be realized for TDF-containing fixed-dose combination products. The potential for cost savings is further inhibited by the introduction of TAF-based co-formulations, which may displace TDF-based combination antiretrovirals.

3.3.1 Additional CDR-Calculated Cost Comparisons

The comparators presented in Table 16 are the initial recommended and alternative ARV regimen options for HIV-1-infected, treatment-naive adults, according to the US DHHS guidelines (updated July 2016),[1] and have been confirmed by the clinical expert.

Costs presented in Table 17 are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table; therefore, these prices may not represent the actual costs to public drug plans.

TABLE 17: CDR COST COMPARISON TABLE FOR ARV AGENTS IN HIV-INFECTED, TREATMENT-NAIVE ADULT PATIENTS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (/Day)	# Pills (/Day)
Emtricitabine/ripivirine/ tenofovir alafenamide fumarate (Odefsey)[a]	**200 mg/ 25 mg/ 25 mg**	**Tab**	**42.3670[b]**	**1 tablet daily**	**42.37**	**1**	**1**
DHHS-Recommended Antiretroviral Regimens							
INSTI-Based Regimens							
Dolutegravir/abacavir/ lamivudine (Triumeq)	50 mg/ 600 mg/ 300 mg	Tab	42.5007	1 tablet daily	42.50	1	1
Dolutegravir (Tivicay) + Emtricitabine/tenofovir disoproxil fumarate (Truvada)	50 mg 200 mg/ 300 mg	Tab	19.0400 29.0797	50 mg daily 1 tablet daily	48.12	1	2
Dolutegravir (Tivicay) + Emtricitabine/tenofovir alafenamide fumarate (Descovy)	50 mg 200 mg/ 25 mg	Tab	19.0400 28.5700[c,d]	50 mg daily 1 tablet daily	47.61	1	2
Elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate (Stribild)	150 mg/ 150 mg/ 200 mg/ 300 mg	Tab	47.2150	1 tablet daily	47.22	1	1
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide fumarate (Genvoya)	150 mg/ 150 mg/ 200 mg/ 10 mg	Tab	46.3893[c,d]	1 tablet daily	46.39	1	1
Raltegravir (Isentress) + Emtricitabine/tenofovir disoproxil fumarate (Truvada)	400 mg 200 mg/ 300 mg	Tab	13.9050 29.0797	400 mg twice daily 1 tablet daily	56.89	2	3

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (/Day)	# Pills (/Day)
Raltegravir (Isentress) + Emtricitabine/tenofovir alafenamine fumarate (Descovy)	400 mg 200 mg/ 25 mg	Tab	13.9050 28.5700[c,d]	400 mg twice daily 1 tablet daily	56.38	2	3
PI-Based Regimens							
Darunavir (Prezista) with ritonavir (Norvir) + Emtricitabine/tenofovir disoproxil fumarate (Truvada)	800 mg 100 mg 200 mg/ 300 mg	Tab	21.7160 1.5183 29.0797	800 mg daily 100 mg daily 1 tablet daily	52.31	1	3
Darunavir (Prezista) with ritonavir (Norvir) + Emtricitabine/tenofovir alafenamide fumarate (Descovy)	800 mg 100 mg 200 mg/ 10 mg	Tab	21.7160 1.5183 28.5700[c,d]	800 mg daily 100 mg daily 1 tablet daily	51.80	1	3
DHHS Alternative Antiretroviral Regimens							
NNRTI-based Regimens							
Efavirenz/tenofovir disoproxil fumarate/emtricitabine (Atripla)	600 mg/ 300 mg/ 200 mg	Tab	44.5627	1 tablet daily	44.56	1	1
Efavirenz (generics) + Emtricitabine/tenofovir alafenamide fumarate (Descovy)	600 mg 200 mg/ 25 mg	Tab	3.8030 28.5700[c,d]	600 mg daily 1 tablet daily	32.37	1	2
Emtricitabine/rilpivirine/ tenofovir disoproxil fumarate (Complera)	200 mg/ 25 mg/ 300 mg	Tab	44.1143	1 tablet daily	44.11	1	1

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (/Day)	# Pills (/Day)
PI-based Regimens							
Atazanavir (Reyataz) with ritonavir (Norvir) + Emtricitabine/tenofovir disoproxil fumarate (Truvada)	300 mg 100 mg 200 mg/ 300 mg	Cap	22.4330[f] 1.5183 29.0797	300 mg daily 100 mg daily 1 tablet daily	53.03	1	3
Atazanavir (Reyataz) with ritonavir (Norvir) + Emtricitabine/tenofovir alafenamide fumarate (Descovy)	300 mg 100 mg 200 mg/ 10 mg	Cap	22.4330[f] 1.5183 28.5700[c,d]	300 mg daily 100 mg daily 1 tablet daily	52.52	1	3
Darunavir/cobicistat (Prezcobix) + Abacavir/lamivudine (generics)	800 mg/ 150 mg 600 mg/ 300 mg	Tab	23.8672 5.9875	1 tablet daily 1 tablet daily	29.85	1	2
Darunavir (Prezista) with ritonavir (Norvir) + Abacavir/lamivudine (generics)	800 mg 100 mg 600 mg/ 300 mg	Tab	21.7160 1.5183 5.9875	800 mg daily 100 mg daily 1 tablet daily	29.22	1	3
Darunavir/cobicistat (Prezcobix) + Emtricitabine/tenofovir disoproxil fumarate (Truvada)	800 mg/ 150 mg 200 mg/ 300 mg	Tab	23.8672 29.0797	1 tablet daily 1 tablet daily	52.95	1	2
Darunavir/cobicistat (Prezcobix) + Emtricitabine/tenofovir alafenamide fumarate	800 mg/ 150 mg 200 mg/ 10 mg	Tab	23.8672 28.5710[c,d]	1 tablet daily 1 tablet daily	52.44	1	2

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (/Day)	# Pills (/Day)
(Descovy)							

ART = antiretroviral therapy; DHHS = Department of Health and Human Services; INSTI = integrase strand transfer inhibitor; PI = protease inhibitor.
Note: All prices are from the Ontario Drug Benefit Formulary (accessed January 2017),[25] unless otherwise indicated.
[a] Currently listed as an alternative initial regimen for ART-naive adults in the DHHS guidelines (accessed January 2017).[1]
[b] Manufacturer's submitted price.
[c] Delta PA, wholesale acquisition price (accessed January 2017).[27]
[d] Not available on any public drug plans.
[f] Saskatchewan Drug Benefit Formulary (accessed January 2017).[28]

4. DISCUSSION

4.1 Summary of Evidence

This submission for FTC/RPV/TAF was filed as a new combination product (funded-components) based on the fact the rilpivirine is funded by a majority of the CDR-participating drug plans (see Appendix 1) and FTC/TAF (Descovy) received a recommendation to reimburse with conditions in August 2016.[10]

FTC/RPV/TAF is indicated as a complete regimen for the treatment of adults infected with HIV-1 with no known mutations associated with resistance to the NNRTI class, tenofovir or FTC, and with a viral load ≤ 100,000 copies/mL.[2] The indications section of the product monograph for FTC/RPV/TAF states that the safety and efficacy of the product has not been established in patients with a prior history of virologic failure.[2] The clinical expert consulted by CADTH indicated that FTC/RPV/TAF is likely to be used in the indicated patient population.

4.2 Bioequivalence

The manufacturer's submission included a summary of one pivotal bioequivalence study (Study 1159 [N = 96]) that compared the individual components of FTC/RPV/TAF against the individual components of two reference products: EVG/COBI/FTC/TAF (Genvoya) and RPV (Edurant). This approach appears to be used because exposure to TAF results in lower levels of plasma of TFV compared with TDF; hence, a comparison with a product such as FTC/RPV/TDF (Complera) would be inappropriate. The use of Genvoya as the reference product involved exposure to two additional active substances (EVG and COBI); however, the clinical expert indicated this did not appear to significantly confound the results of the study. Nevertheless, it is uncertain why the manufacturer did not use Descovy (FTC/TAF) as the reference product for evaluating the bioequivalence of FTC and TAF. Reviewers for Health Canada concluded that the bioavailability of FTC, TAF, and RPV following administration of the Odefsey tablets is comparable to the bioavailability of FTC and TAF following administration of Genvoya and RPV following administration Edurant.[4,5] Reviewers for the FDA and EMA indicated that bioequivalence criteria were met for each of the individual components (i.e., FTC, RPV, and TAF).[6,7] Reviewers for the EMA noted that there is no evidence to suggest that exposure to TDF instead of TAF would increase the risk of resistance.[6]

4.3 Efficacy

The efficacy data provided in the manufacturer's submission were derived from seven phase III studies and two phase IIIb studies. The phase three RCTs were all conducted using products other than FTC/RPV/TAF and included the following: four trials conducted using EVG/COBI/FTC/TAF (Genvoya), including two studies comparing EVG/COBI/FTC/TAF (Genvoya) with EVG/COBI/FTC/TDF (Stribild) in treatment-naive patients (Study 104 [N = 872] and Study 111 [N = 872]), one trial comparing Genvoya with TDF/FTC plus a third agent (Study 109 [N = 1443]) in virologically supressed adults, and one uncontrolled trial conducted in adults with mild to moderate renal failure (Study 112 [N = 248]); two phase III studies comparing RPV (Edurant) with EFV in combination with FTC/TDF (ECHO [N = 694]) or FTC/TDF, AZT/3TC or ABC/3TC (THRIVE [N = 680]); one phase three switching study comparing FTC/RPV/TDF (Complera) with the patient's prior treatment regimen (SPIRIT [N = 476]). The majority of the phase III studies that were included in the review have been previously reviewed by CADTH in the CDR submissions for Genvoya, Descovy, and Edurant.[8-10]

The two phase IIIb studies evaluated switching to FTC/RPV/TAF from FTC/RPV/TDF (Study 1216 [N = 632]) or EFV/TDF/FTC (Study 1160 [N = 881]). Studies 1160 and 1216 demonstrated that switching to FTC/RPV/TAF was noninferior to remaining on treatment with Atripla or Complera (respectively) for virologic success at 48 weeks.[12,13] The manufacturer reported that the results for these studies were not available at the time of the Health Canada submission; therefore, no efficacy or safety data were available from RCTs of FTC/RPV/TAF in HIV-infected patients at the time of regulatory filing. The indications for use in treatment-naive and virologically suppressed patients are based on the efficacy demonstrated in the phase three studies that were conducted using Genvoya, Edurant, and Complera.

4.4 Harms

Patients enrolled in studies 1160 and 1216 were required to have been on a stable regimen of Atripla or Complera for at least six consecutive months prior to screening; therefore, the study population was enriched with those who were able to tolerate Atripla and Complera. Patients with hepatitis B or hepatitis C co-infection were excluded from studies 1160 and 1216,[12,13] as well as the pivotal studies for Genvoya, Edurant, and Complera.[23,29-32] The Canadian product monograph for FTC/RPV/TAF has a black box warning stating that the safety and efficacy has not been established in patients co-infected with HIV-1 and HBV and that discontinuation of FTC/RPV/TAF in these patients may be associated with severe acute exacerbations of hepatitis.[2] The product monograph recommends that patients co-infected with HIV-1 and HBV who discontinue FTC/RPV/TAF should have clinical and laboratory monitoring for at least several months after treatment is discontinued.[2] The product monograph states that this is due to the FTC and/or TAF components of FTC/RPV/TAF. Similar warnings appear in the product monographs of many other FDC products approved in Canada, including those that contain FTC/TAF (i.e., Genvoya and Descovy),[33,34] FTC/TDF (i.e., Stribild, Truvada, Atripla, and Complera),[14,15,35,36] and those that contain lamivudine (Triumeq).[37]

Percentage change from baseline in hip and spine BMD were pre-specified key secondary endpoints in both studies 1160 and 1216. At the 48-week interim analysis, both studies demonstrated a statistically significant improvement from baseline in BMD at the hip and spine in patients who switched from to FTC/RPV/TAF compared with those who continued to be treated with Complera or Atripla ($P < 0.001$ for spine and hip BMD in both studies). The product monograph for FTC/RPV/TAF states that the effects of

TAF-associated changes in BMD on long-term bone health and future fracture risk are unknown.[2] Recommendations for BMD monitoring are similar in the product monographs for FTC/RPV/TAF, Complera, and Atripla, indicated that monitoring should be considered for patients who have a history of pathologic bone fracture or are at risk for osteopenia.[2,14,15] The clinical expert consulted by CDR indicated that switching to a TAF-containing regimen would not result in a reduced need for monitoring of BMD in those who require routine monitoring.

There was also a significant difference in change from baseline in eGFR favouring FTC/RPV/TAF over Complera at 48 weeks in Study 1216.[13] In contrast, there was a statistically significant decrease in eGFR for patients who switched from Atripla to FTC/RPV/TAF at 48 weeks in Study 1160.[12] The manufacturer reported that this decrease is likely associated with the initiation of treatment involving RPV, which is not a component of Atripla, and is known to reduce tubular secretion of creatinine. Baseline eGFR was lower in Study 1216, where patients had been receiving treatment with the RPV-containing Complera compared with Study 1160, where patients had been receiving treatment with Atripla (mean eGFR 106.2 mL/min and 113.6 mL/min, respectively).[12] Compared with Atripla and Complera, the manufacturer reported that patients who switched to FTC/RPV/TAF demonstrated statistically significant reductions in proteinuria, albuminuria, and tubular proteinuria.

Patients require the use of HIV antiviral treatment for their lifetime and indicated that they value the improved safety profile of TAF-containing regimens compared with TDF-containing regimens, with respect to fewer renal adverse events and a reduction in the loss of BMD.

4.5 Other Considerations

In the patient group input received for this submission, some individuals expressed a reluctance to switch to TAF based regimens. These patients cited their satisfaction with the effectiveness and safety profile of their current HIV treatment regimen(s) as their primary reason for not wanted to switch medications.

FTC/RPV/TAF is administered as one tablet taken once daily with food. The clinical expert consulted by CDR indicated that patients generally prefer to take HIV medications with food as it is often more convenient and more tolerable than administering treatments at night on an empty stomach (e.g., Atripla).

4.6 Potential Place in Therapy[2]

In Canada, there are some thirty licensed individual or co-formulated HIV antivirals.[16] The majority of patients being treated for HIV will have a more or less "wild type" virus, that is, one that is generally free of drug resistance mutations and therefore will respond to most available antivirals.[17]

The selection of the most appropriate treatment for patients is individualized based on patient lifestyle, tolerance, and virus type. The clinical expert consulted by CADTH for this review indicated that there are practice variabilities across Canada based on physician experience with the available agents, however, the ideal combinations are potent (effectively suppress HIV replication), convenient (STRs versus multi-tablet regimens, once daily dosing, no food requirements), and tolerable in the short and long term.[18] STRs are preferred by most patients, and likely improve adherence and therefore effectiveness. There are five STRs available in Canada: Atripla, Complera, Stribild, Genvoya, and Triumeq. Atripla, Complera and Stribild include TDF, and may therefore be considered less favourable due to their potential for long term renal dysfunction and BMD loss. Genvoya contains TAF instead of TDF, and consequently has less potential for these toxicities; however, Genvoya has numerous drug-drug interactions (DDIs) and should be taken with food. Triumeq does not contain tenofovir, so the renal and bone toxicities are not a concern, it is very tolerable, can be taken with or without food, and has almost no DDIs. However, a small proportion of patients[19] will experience a hypersensitivity reaction to the abacavir component of Triumeq, and concerns remain about the potential cardiotoxicity of abacavir.[20,21]

Treatment for patients in the form of multi-tablet regimens may also be considered. Isentress, Edurant and Tivicay are all free of most DDIs, and have been found to be effective and tolerable. Used in combination with Descovy, there would be few expected short or long term side effects; used in combination with Kivexa, the major consideration would be the potential for cardiotoxicity. Finally, Prezcobix also may be used with Descovy or Kivexa, however, these combinations have the potential for DDIs.

In summary, it can be seen that there are many options for therapy for wild type HIV.

FTC/RPV/TAF has its advantages, but it does not fill any major unmet need. It would most likely be used in substitution for Complera.

4.7 Cost

The manufacturer submitted a cost comparison of drug costs for FTC/RPV/TAF compared with its individual components (RPV + FTC/TAF) and other ARV regimens. At the submitted daily price of $42.37 per tablet, FTC/RPV/TAF is cost saving (approximately $1 daily) compared to the sum of the costs of its individual components (RPV + FTC/ TAF; $43.71 daily), and it is less costly than other DHHS-alternative STRs ($44.11 to $44.56 daily). In comparison with DHHS-preferred STRs, the daily cost of FTC/RPV/TAF is similar to DTG/ABC/3TC ($42.50 daily) and lower than the cost of other DHHS-preferred STRs ($46.39 to $47.22 daily). While the daily cost of several DHHS-alternative regimens is lower than the daily cost of FTC/RPV/TAF, these treatment options comprise multi-tablet ARV regimens.

[2] This information is based on information provided in draft form by the clinical expert consulted by CADTH for the purpose of this review.

5. CONCLUSION

FTC/RPV/TAF is indicated as a complete regimen for the treatment of adults infected with HIV-1 with no known mutations associated with resistance to the NNRTI class, tenofovir or FTC, and with a viral load of ≤ 100,000 copies/mL. The manufacturer's submission included a summary of one pivotal bioequivalence Study (Study 1159 [N = 96]) which demonstrated that the individual components of FTC/RPV/TAF were bioequivalent to the individual components of two reference products: EVG/COBI/FTC/TAF (Genvoya) and RPV (Edurant). The results of the bioequivalence study were used to bridge the efficacy and safety data of Edurant, Genvoya, and Complera to support market authorization of FTC/RPV/TAF.

The efficacy data provided in the manufacturer's submission were derived from seven completed phase III studies and interim data from two phase IIIb studies. The majority of the phase III studies that were included in the review have been previously reviewed by CADTH in the CDR submissions for Genvoya, Descovy, and Edurant. The two phase IIIb studies evaluated switching to FTC/RPV/TAF from FTC/RPV/TDF (Study 1216 [N = 632]) or EFV/TDF/FTC (Study 1160 [N = 881]). Studies 1160 and 1216 demonstrated that switching to FTC/RPV/TAF was noninferior to remaining on treatment with Atripla or Complera (respectively) for virologic success at 48 weeks.

Percentage change from baseline in hip and spine bone mineral density (BMD) were pre-specified key secondary endpoints in both studies 1160 and 1216. At the 48-week interim analysis, both studies demonstrated a statistically significant improvement from baseline in BMD at the hip and spine in patients who switched from Complera or Atripla to FTC/RPV/TAF compared with those who continued to be treated with Complera or Atripla ($P < 0.001$ for spine and hip BMD in both studies). The effects of TAF-associated changes in BMD on long-term bone health and future fracture risk are currently unknown.

At the submitted daily price of $42.37 per tablet, FTC/RPV/TAF is less costly than the sum of its individual components, RPV ($15.14 daily) and FTC/TAF ($28.57 daily), and is less costly than other DHHS-alternative STRs, including FTC/RPV/TDF ($44.11 daily).

APPENDIX 1: DRUG PLAN LISTING STATUS FOR INDIVIDUAL COMPONENTS

TABLE 18: LISTING STATUS FOR INDIVIDUAL COMPONENTS OF THE NEW COMBINATION PRODUCT

Components	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Emtricitabine	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB
Rilpivirine	-	FB	RES	RES	FB	FB	FB	FB	RES	RES	NA	FB	FB	NA
Tenofovir alafenamide fumarate	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB
Relevant Comparator(s)														
Complera	FB	FB	RES	RES	FB	FB	FB	FB	RES	RES	FB	FB	FB	FB

AB = Alberta; BC = British Columbia; DND = Department of National Defence; EX = Exception item for which coverage is determined on a case-by-case basis; FB = full benefit; MN = Manitoba; NA = not available; NB = not a benefit; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; RES = Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit); SK = Saskatchewan; UR = under review; VAC =Veterans Affairs Canada; YK = Yukon.

TABLE 19: RESTRICTED BENEFIT CRITERIA FOR RILPIVIRINE FOR THE TREATMENT OF HIV

Drug Plan	Criteria for Restricted Benefit
Saskatchewan	For management of HIV disease. This drug, as with other antivirals in the treatment of HIV, should be used under the direction of an infectious disease specialist.
Manitoba	For the treatment of HIV-1-infected treatment-naive patients.
Newfoundland and Labrador	For the treatment of HIV-1 infection in treatment-naive patients, when used in combination with other antiretroviral agents.
Yukon	When prescribed by an infectious disease specialist.

HIV-1 = human immunodeficiency virus type 1.

TABLE 20: BENEFIT CRITERIA FOR COMPLERA (EMTRICITABINE/RILPIVIRINE/TENOFOVIR DISOPROXIL FUMARATE) FOR THE TREATMENT OF HIV-1

Drug Plan	Criteria for Restricted Benefit
Saskatchewan	For the treatment of HIV-1 in antiretroviral treatment-naive patients, or to replace the three components given as dual or triple therapy. This drug, as with other antivirals in the treatment of HIV, should be used under the direction of an infectious disease specialist.
Manitoba	For the treatment of HIV-1 in antiretroviral treatment-naive patients, or to replace the three components given as dual or triple therapy for patients stabilized on appropriate doses.
Newfoundland and Labrador	For the treatment of HIV-1 in antiretroviral treatment-naive patients, or to replace the three components given as dual or triple therapy for patients stabilized on appropriate doses.
Yukon	As a complete regimen for antiretroviral treatment-naive HIV-1 infected patients in whom efavirenz is not indicated.

HIV-1 = human immunodeficiency virus type 1.

APPENDIX 2: SUMMARY OF PATIENT INPUT

This section was summarized by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Canadian Treatment Action Council (CTAC) is a national non-governmental organization addressing access to holistic treatment, care, and support for people living with human immunodeficiency virus (HIV) and hepatitis C (HCV). Its goals are to engage community members, service providers, policy-makers, and other relevant stakeholders to identify, develop, and implement policy and program solutions. Full CTAC membership is reserved for: a) individuals living with HIV (including HCV co-infection); b) organizations, groups, or projects with a substantial HIV mandate (including HCV co-infection).

CTAC received unrestricted organizational and educational grants from the following in the 2016-2017 fiscal year: Abbott/Abbvie, Gilead Sciences, and ViiV Healthcare. CTAC receives grant funding from the Public Health Agency of Canada to conduct patient input activities; the above mentioned industry groups are not directly involved in the development of CTAC's patient input submissions.

2. Condition Related Information

Information was gathered via a national consultation webinar that provided an overview of the patient input process used by CADTH and reviewed the key findings from the FTC/RPV/TAF clinical trials. The webinar was attended by three participants who identified themselves as HIV-positive (two males and one female). The participants were asked to complete a survey after the webinar to gather additional information. This was supplemented by the survey data that was collected by CTAC for the patient group input submissions for Descovy (FTC/TAF) and Genvoya (EVG/COBI/FTC/TAF).

HIV is a serious, life-threatening disease that compromises a patient's immune system and, if left untreated, predisposes these patients to opportunistic infections. Highly active antiretroviral treatment (HAART) is the mainstay for HIV management. For the most part, patients taking HAART achieve viral suppression (an undetectable viral load), whereby there are less than 50 copies/mL in a blood sample. Hence, patients with HIV manage their disease as a chronic illness. However, patients with HIV often tend to experience "accelerated aging" and become more susceptible to inflammatory and non-infectious comorbidities such as cardiovascular (CV), kidney, and liver disease, along with bone fractures.

Patients living with HIV often experience negative mental health outcomes. These can be due to the side effects from treatment or from social stigma, discrimination, and related stress. Mental health issues and stigma were noted by the respondents, including challenges encountered in the work place and accessing the health care system:

"In the past, my biggest challenge has been to explain to my employer periodic requests to make adjustments to my work schedule in order to seek medical advice and treatment - especially when I had consultations and follow-ups with my family doctor, ID specialist, nephrologist, ENT specialist and GI specialist within the same general period of time. My health challenges were most certainly linked with side effects to my treatment at the time."

"No doctor in our area wants to take on HIV+ patients on a full time basis and when we seek counselling advice we are told we would have a much better life if we moved back to Toronto"

The most common physical symptom associated with HIV is fatigue, which also happens to be one of the main side effects of HAART treatment.

In addition to both mental and physical side effects, patients with HIV often experience stress, hardship, and access difficulties associated with the disease and treatments. For instance, access to affordable treatment remains difficult for many patients, as are the complications associated with access to treatment when moving between provinces. Additionally, since HIV is treated in a multifaceted way, most often with collaboration between different specialists, adherence programs, and outreach programs, stress is often compounded when trying to obtain proper care.

Caregivers can be negatively affected in many ways. They are often responsible for or aid in the travel associated with treatment. They echo the above patient's comments regarding the monetary hardships due to treatment costs or required travel, especially when living in remote areas, and they are often the main persons (aside from the patient) ensuring adherence to medication. In addition, the peace of mind of the caregivers can be negatively affected when they see their loved ones experience treatment side effects and constantly have to encourage them to adhere to their treatment regimen.

3. Current Therapy Related Information

CTAC emphasized that HIV is a complex illness and people have different responses to currently available treatments. The majority of those living with HIV are able to achieve viral suppression by working with their health care providers to find effective therapeutic regimens. However, there remains an unmet need as some people living with HIV are unable to achieve viral suppression, despite attempts with multiple different treatment regimens. Additionally, CTAC noted that adherence to HIV therapeutic regimens is necessary for treatments to be effective. Treatment adherence (specifically taking the medication when prescribed, as prescribed) is particularly important with regard to HIV treatment as nonadherence can lead to drug class resistance. Once this occurs, it is necessary for the patient to embark on a different treatment regimen. Therefore, patients note that having many options available is of the utmost clinical importance.

Patients reported current or previous treatment experience with a variety of different treatments. Many respondents indicated that HIV treatment has resulted in noticeable improvements in their quality of life and their ability to participate in daily activities:

"Health life and work life has improved. I am [able] to work and be in a healthy relationship as well."

Respondents noted that although their treatment was effective at suppressing their viral load, there are side effects that have a negative impacted on their quality of life, as highlighted by one respondent:
"*my viral load has been undetectable since within one month of commencing treatment in 2009. Until my current ARV regimen, health complications resulting from the toxicity of previous Rx medications were hepatic and renal deterioration. Hypercholesterolemia and bone density loss are also suspected collateral damage."*

4. Expectations about the Drug being Reviewed

Patients noted that TAF may be associated with fewer renal issues and a reduction in the loss of BMD compared with TDF. This improvement in the adverse event profile was considered to be important for patients, who require the use of HIV antiviral treatment for their lifetime. Patients who expressed a reluctance to switch to TAF based regimens cited their satisfaction with the effectiveness and safety profile of their current regimens as a reason not to switch medications.

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