Common Drug Review
Clinical Review Report

August 2016

Drug	Emtricitabine/tenofovir alafenamide fumarate (Descovy)
Indication	In combination with other antiretrovirals (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients 12 years of age and older (and weighing ≥ 35 kg)
Listing request	For use in combination with other antiretrovirals for treatment of treatment-naive and virologically suppressed HIV-1 infected adult and pediatric patients 12 years of age and older.
Dosage form(s)	emtricitabine/tenofovir alafenamide fumarate (200/10 mg) and emtricitabine/tenofovir alafenamide fumarate (200/25 mg) fixed-dose combination (oral tablet)
NOC date	April 29, 2016
Manufacturer	Gilead Sciences Canada, Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AE	adverse event
ANOVA	analysis of variance
ART	antiretroviral therapy
ARV	antiretroviral
ATV/r	ritonavir-boosted atazanavir
CI	confidence interval
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
COBI	cobicistat
CSR	Clinical Study Report
CTAC	Canadian Treatment Action Council
DHHS	US Department of Health and Human Services
DRV/r	ritonavir-boosted darunavir
DTG	dolutegravir
DXA	dual X-ray absorptiometry
EFV	efavirenz
$eGFR_{CG}$	estimated glomerular filtration rate according to the Cockcroft–Gault formula
EVG	elvitegravir
EVG/COBI/FTC/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (Genvoya)
EVG/COBI/FTC/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild)
FAS	full analysis set
FTC	emtricitabine
FTC/TAF	emtricitabine/tenofovir alafenamide fumarate (Descovy)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (Truvada)
HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HRQoL	health-related quality of life
LSM	least squares mean
NI	non-inferiority
NNRTI	non-nucleoside reverse transcriptase inhibitor
OL	open-label
PK	pharmacokinetic
PP	per-protocol

RAL	raltegravir
RCT	randomized controlled trial
RNA	ribonucleic acid
RPV	rilpivirine
SAE	serious adverse event
SD	standard deviation
TAF	tenofovir alafenamide fumarate
TBLH	total body less head
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
URTI	upper respiratory tract infection
VL	viral load

EXECUTIVE SUMMARY

Introduction

The current standard of care for human immunodeficiency virus (HIV) management is to treat patients with a combination of antiretroviral (ARV) drugs with the primary goal of achieving and maintaining maximal suppression of viral load, leading to restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.

Emtricitabine/tenofovir alafenamide fumarate (FTC/TAF) has a proposed Health Canada indication for use in combination with other ARVs (such as non-nucleoside reverse transcriptase inhibitors [NNRTIs] or protease inhibitors) for the treatment of HIV-1 infection in adult and pediatric patients 12 years of age and older (and weighing ≥ 35 kg). FTC/TAF is a single-tablet, fixed-dose combination(FDC) of two nucleoside reverse transcriptase inhibitors (NRTIs) that is available in two dosage forms: FTC/TAF 200 mg/10 mg, or FTC/TAF 200 mg/25 mg. The 200 mg/10 mg dose is recommended when FTC/TAF is used in combination with an HIV-1 protease inhibitor that is boosted by either ritonavir or cobicistat (COBI); otherwise, the recommended dose of FTC/TAF is 200 mg/25 mg. FTC/TAF is similar in nature to emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) (Truvada); however, FTC/TAF contains the prodrug TAF instead of the prodrug TDF. FTC/TDF (Truvada) was recommended for reimbursement by the CADTH Canadian Drug Expert Committee (CDEC) in December 2008 as an alternative in the initial phase of treatment for adult patients with HIV infection who have experienced intolerance or adverse events (AEs) with other nucleoside combinations, including lamivudine in combination with zidovudine, abacavir, stavudine, or didanosine, and who have not developed virologic failure or clinical progression on initial antiretroviral therapy (ART).[1]

The components of FTC/TAF are also part of a single-tablet regimen — elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/COBI/FTC/TAF, Genvoya) — that has a Health Canada indication for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older (weighing ≥ 35 kg) with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF. EVG/COBI/FTC/TAF is similar in nature to elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF, Stribild), except that the prodrug TDF has been replaced with the prodrug TAF. EVG/COBI/FTC/TAF (Genvoya) was recommended for reimbursement by CDEC in March 2016 as per the Health Canada indication.

Indication under review
For use in combination with other antiretrovirals (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients 12 years of age and older (and weighing ≥ 35 kg).
Listing criteria requested by sponsor
For use in combination with other antiretrovirals for treatment of treatment-naive and virologically-suppressed HIV-1 infected adult and pediatric patients 12 years of age and older.

The objective of this systematic review was to evaluate of the beneficial and harmful effects of the fixed-dose combination of FTC/TAF in combination with other ARVs for the treatment of HIV-1 infection in adult and pediatric patients 12 years of age and older (and weighing ≥ 35 kg).

Results and Interpretation

Included Studies

The evidence for this review was drawn from six studies. Five of the six studies [2-6] were reviewed in the CADTH Common Drug Review (CDR) submission for EVG/COBI/FTC/TAF (Genvoya). The inclusion of studies evaluating the FTC/TAF-based ART regimen EVG/COBI/FTC/TAF was based on evidence from two bioequivalence studies. These studies were randomized, open-label, single-dose, two-way crossover phase 1 studies (study 1472[7] and study 1473[8]) that evaluated the bioequivalence of FTC and TAF between: FTC/TAF fixed-dose combination + EVG + COBI[7] or FTC/TAF fixed-dose combination[8] and EVG/COBI/FTC/TAF. The FTC and TAF components of FTC/TAF + EVG + COBI[7] or FTC/TAF fixed-dose combination[8] were found to be bioequivalent to the FTC and TAF components of EVG/COBI/FTC/TAF. The sixth study was not included in the CDR submission for EVG/COBI/FTC/TAF.

The six included studies consisted of three phase 3 multi-centre, double-blind, double-dummy, active-controlled, non-inferiority trials comparing an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) to an FTC/TDF-based regimen (EVG/COBI/FTC/TDF) (study 104, n = 872; study 111, n = 872), and comparing FTC/TAF + a third drug to FTC/TDF + a third drug (study 1089, n = 663); one phase 3, multi-centre, open-label, active-controlled, non-inferiority trial comparing an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) to an FTC/TDF-based regimen (FTC/TDF + a third drug) (study 109, n = 1443); and two multi-centre, open-label, single-arm studies assessing an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) in adult patients with reduced kidney function (study 112, n = 252) and in adolescent patients (study 106, n = 48). The primary efficacy outcome for all studies was the percentage of patients with HIV-1 ribonucleic acid (RNA) < 50 copies/mL at week 48 (studies 104, 111, 109, and 1089) or week 24 (studies 112 and 106) using the FDA-defined snapshot algorithm. The non-inferiority margin in studies 104, 111, and 109 was 12%, which is accepted by the FDA; the non-inferiority margin in study 1089 was 10%. Superiority was also assessed if non-inferiority was established in all four randomized controlled trials (RCTs).

Studies 104 and 111 enrolled exclusively treatment-naive adults, whereas studies 1089 and 109 enrolled only virologically suppressed adults who had been on an FTC/TDF-based regimen (FTC/TDF + a third drug). There were no direct comparative data available for FTC/TAF-based regimens against dolutegravir/abacavir/lamivudine (DTG/ABC/3TC), which is another US Department of Health and Human Services (DHHS)–preferred initial regimen available in Canada.

Studies 112 and 106 evaluated the efficacy and safety of an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) in HIV-infected adults with mild to moderate renal impairment (study 112) (for which the majority of patients were virologically suppressed; n = 242, 97.6%), and in treatment-naive adolescents (study 106) (n = 48), respectively.

Efficacy

In studies 104, 111, and 1089, FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) were non-inferior (NI margin 10% or 12%) to FTC/TDF-based regimens (EVG/COBI/FTC/TDF or FTC/TDF + a third drug) with respect to the percentage of patients with HIV-1 RNA < 50 copies/mL at week 48 for both treatment-experienced (study 1089) and treatment-naive patients (studies 104 and 11) (Table 1, Table 2).

Study 104 and study 111 compared an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) to an FTC/TDF-based regimen (EVG/COBI/FTC/TDF) and found a response rate (percentage of patients with HIV-1 RNA <50 copies/mL), based on a per-protocol analysis, of 97.8% versus 98.0% and 97.2% versus 95.4%, respectively, at week 48.

In study 109, results from the primary analysis showed that for those patients who switched to an FTC/TAF-based regimen (EVG/COBI/FTC/TAF), the percentage of patients who achieved an HIV-1 RNA < 50 copies/mL was non-inferior to the percentage of patients who achieved an HIV-1 RNA < 50 copies/mL while remaining on their pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug) at week 48 (99.1% versus 98.9%; per-protocol [PP] analysis). Further analysis (based on the full analysis set [FAS]) demonstrated that a statistically significantly greater percentage of patients on the FTC/TAF-based regimen (EVG/COBI/FTC/TAF) relative to the FTC/TDF-based regimen (FTC/TDF + a third ARV drug) achieved a viral load [VL] < 50 copies/mL at week 48 (4.1% (1.6, 6.7); *P* = 0.0002) (Table 2).

Study 1089 compared FTC/TAF-based regimens (FTC/TAF + a third drug) to FTC/TDF-based regimens (FTC/TDF + a third drug) and found a response rate (percentage of patients with HIV-1 RNA < 50 copies/mL), based on an intention-to-treat (ITT) analysis, of 94.3% versus 93% at week 48. No PP analysis results were reported.

In study 112, the primary analysis demonstrated that the virologic success rates at 24 weeks among adult patients where the majority (97.6%) switched to an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from their existing ART regimen were numerically similar between patients with estimated glomerular filtration rate according to the Cockcroft–Gault formula [$eGFR_{CG}$] < 50 mL/min and patients with $eGFR_{CG}$ ≥ 50 mL/min (95.0% and 95.1%, respectively) (Table 3). In study 106, the virologic success rate at 24 weeks was 91.3% for 23 ART-naive adolescents receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF). Due to the lack of a comparator arm in both studies (study 112 and 106), the relative efficacy and safety of an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) against other ART regimens in adult patients with mild to moderate renal impairment and in treatment-naive adolescents is unknown. In addition, given the small sample sizes for treatment-naive adult patients with mild to moderate renal impairment (n = 6) and for treatment-naive adolescents (n = 23), the results were insufficient to draw robust conclusions about the efficacy and safety of the FTC/TAF-based regimen (EVG/COBI/FTC/TAF) in these populations.

Very few patients (n = 14, 0.4%) developed primary genotypic resistance through week 48 in the four RCTs. In studies 112 and 106, through week 48, no patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) developed new resistance or mutations that were not already present at baseline. Further, there were no differences in health-related quality of life (HRQoL) among patients receiving FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug), both as a change from baseline, and compared with FTC/TDF-based regimens (EVG/COBI/FTC/TDF or FTC/TDF + a third drug). Across all studies, at least 77% of patients in each treatment arm achieved adherence rates of ≥ 95%.

Harms

Across all six studies, at least 80% of patients in each trial experienced at least one treatment-emergent adverse event (TEAE). Diarrhea (9% to 19%), nausea (< 5% to 23%), upper respiratory tract infections (URTIs) (9% to 17%), and headache (7% to 17%) appeared to be the most common AEs reported by patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF or FTC/TAF + a third drug). The percentage of patients who experienced a serious adverse event (SAE) while receiving FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) varied. Across the four RCTs, fewer patients receiving FTC/TAF-based regimens withdrew due to AEs (0.7% to 0.9%) than those receiving an FTC/TDF-based regimen (0% to 2.5%) except in study 1089, where more patients receiving an FTC/TAF-based regimen (2.1%) withdrew due to AEs than those receiving an FTC/TDF-based regimen (0.9 %). There were two deaths reported in study 104 (one in each treatment group) and three in study 111 (one in the FTC/TAF-based regimen group). In study 109, four patients who switched to an FTC/TAF-based regimen

(EVG/COBI/FTC/TAF) from a pre-existing regimen of FTC/TDF + a third drug died. In study 1089, one patient who switched to an FTC/TAF-based regimen from a pre-existing regimen of FTC/TDF + a third drug died; no patients died in the comparator group. None of the reported deaths were considered treatment-related. There were no deaths in studies 112 and 106.

Exposure to FTC/TDF-based regimens (EVG/COBI/FTC/TDF, or FTC/TDF + a third drug) has been shown to reduce kidney function in some patients with HIV, although these changes rarely warrant discontinuation from therapy, according to the clinical expert consulted for this review. Treatment-naive patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) had a smaller reduction in kidney functioning from baseline to week 48 relative to patients receiving an FTC/TDF-based regimen (EVG/COBI/FTC/TDF) in studies 104 and 111 (as measured by a decrease in median $eGFR_{CG}$). The median treatment group difference was 3.6 mL/min in study 104, and 6.2 mL/min in study 111 in favour of the FTC/TAF-based regimen (EVG/COBI/FTC/TAF). In study 109, median $eGFR_{CG}$ increased slightly (1.8 mL/min) from baseline among patients who switched to a FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from a pre-existing FTC/TDF-based regimen (FTC/TDF + a third ARV drug), but decreased (–3.7 mL/min) among patients who stayed on their pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug), resulting in a statistically significant difference between groups (median difference 5.5 mL/min, $P < 0.001$) in favour of the FTC/TAF-based regimen (EVG/COBI/FTC/TAF).

In study 1089, renal function improved in both treatment arms, with patients in the FTC/TAF-based regimen arm (FTC/TAF + a third drug) having a statistically significant improvement in renal function compared with patients in the FTC/TDF-based treatment arm (FTC/TDF + a third drug) (median difference: 5.6 mL/min, $P < 0.001$). In study 112, among virologically suppressed adults, overall kidney function appeared to decrease at 24 weeks, although the effect seemed to differ by severity of kidney impairment at baseline. The trend for decreased overall kidney function was also evident from baseline to week 24 among treatment-naive adolescents receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) in study 106. The clinical expert involved in this review indicated that the magnitude of the changes in kidney function and the differences between treatment groups across studies were not likely to be clinically meaningful, but may be important in the long term.

HIV-infected individuals experience accelerated bone loss compared with the general population, especially with TDF exposure; however, the risk of fracture is low, according to the clinical expert consulted by CDR. In studies 104 and 111, treatment-naive adult patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) had a smaller mean percentage reduction in bone mineral density (BMD) in the hip and spine from baseline to week 48 compared with FTC/TDF-based regimens (EVG/COBI/FTC/TDF). This difference was statistically significant in both studies (study 104: hip BMD least squares mean [LSM] difference: 2.4 [1.9, 2.9], $P < 0.001$; spine BMD LSM difference 1.6 [1.2, 2.1], $P < 0.001$; study 111: hip BMD LSM difference 2.2 (1.7, 2.6), $P < 0.001$; spine BMD LSM difference 1.5 [1.1, 1.9], $P < 0.001$). In studies 109 and 1089, there was a statistically significant increase in the per cent change in mean hip and spine BMD from baseline to week 48 in virologically suppressed adult patients who switched to a FTC/TAF-based regimen (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) compared with patients who stayed on their pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug) (study 109: hip BMD LSM difference 1.8 [1.5, 2.1], $P < 0.0001$; spine BMD LSM difference 2.0 [1.6, 2.5], $P < 0.0001$; study 1089: hip BMD LSM difference 1.3 [0.9, 1.7], $P < 0.001$; spine BMD LSM difference 1.7 (1.2, 2.2), $P < 0.001$). In study 112, the overall mean BMD of the hip and spine increased in patients who switched to an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from their pre-existing ART regimen. The clinical expert involved in this review indicated that the magnitude of the changes (across all studies) in BMD were not likely to be clinically meaningful, but may be important in the long term.

Place in Therapy

The standard of care for antiviral therapy for HIV typically consists of a "backbone" of two NRTIs, which is generally ABC/3TC (Kivexa) or FTC/TDF (Truvada) combined with another antiviral drug (with or without a booster – for example, COBI or ritonavir).[9] ABC/3TC is hindered by the requirement for genetic testing for HLA B5701 prior to its use,[10,11] the possibility of reduced effectiveness at higher VLs,[12] and the association in some studies with myocardial infarctions.[13] As such, FTC/TDF is the most commonly used antiviral backbone. FTC/TDF is very well tolerated, but BMD may decline in some patients,[14] and there is some evidence for renal phosphate wasting or renal failure.[15]

FTC/TAF is the newest backbone co-formulation therapy, which achieves lower plasma levels of tenofovir, leading to fewer effects on renal function or BMD, but with effectiveness for suppression of HIV replication comparable to that of FTC/TDF. Moreover, there are no expected pharmacokinetic or pharmacodynamic differences between FTC/TAF and FTC/TDF. It is very likely that FTC/TAF will replace FTC/TDF in almost all patients with HIV infection. The exceptions to this would be:

- in patients receiving post-exposure prophylaxis after potential HIV exposure, where the duration of therapy is only 28 days and therefore, the long-term renal and bone toxicities of FTC/TDF would be negligible, and,
- in pre-exposure prophylaxis, where human data documenting the effectiveness of FTC/TAF are unavailable.

Each of the backbone co-formulation therapies (ABC/3TC, FTC/TDF, and FTC/TAF) may be given in combination with another ARV drug as a multi-tablet regimen, or may be co-formulated with other ARVs as a single-tablet regimen (EFV/TDF/FTC, FTC/RPV/TDF, EVG/COBI/FTC/TDF, DTG/ABC/3TC, and EVG/COBI/FTC/TAF). Single-tablet regimens are the preferred therapy for the majority of patients given their convenience. However, for patients who have viral resistance, comorbidities, or drug interactions, a multi-tablet regimen may be indicated. As such, a fraction of patients, approximately 10% to 15% (according to the clinical expert involved in the review), will be on FTC/TDF as a backbone therapy (in combination with another ARV drug), as opposed to the alternative backbone, ABC/3TC, or a single-tablet regimen, and will be eligible for treatment with FTC/TAF.

Conclusions

The evidence for the efficacy and safety of FTC/TAF-based regimens was based on data from studies that included two formulations: EVG/COBI/FTC/TAF and FTC/TAF + a third drug. The FTC and TAF components in the single-tablet regimen (EVG/COBI/FTC/TAF) were found to be bioequivalent to the FTC and TAF components of FTC/TAF as a fixed-dose combination and FTC/TAF administered simultaneously with EVG and COBI.

FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) were shown to be non-inferior to FTC/TDF-based regimens (EVG/COBI/FTC/TDF or FTC/TDF + a third drug) in suppressing VL among treatment-naive and treatment-experienced adults after 48 weeks of treatment. FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) were associated with relatively similar rates of AEs as FTC/TDF-based regimens in the included studies, among which diarrhea, nausea, URTIs, and headache appeared to be the most common. FTC/TAF-based regimens showed a statistically significant comparative benefit with respect to kidney functioning (eGFR) and bone health (BMD) compared with FTC/TDF-based regimens; however, the observed changes are unlikely to be clinically meaningful in the short term, and are of uncertain importance with respect to the risks of kidney failure and bone fracture in the long term.

There were no comparative efficacy and safety data available for FTC/TAF-based regimens compared with FTC/TDF-based regimens in adult patients with mild to moderate kidney impairment or in adolescents. The clinical efficacy and safety of FTC/TAF-based regimens in these populations are uncertain.

TABLE 1: SUMMARY OF RESULTS — TREATMENT-NAIVE ADULTS (RANDOMIZED CONTROLLED TRIALS)

		Study 104		Study 111	
		EVG/COBI/FTC/TAF (N = 435)	EVG/COBI/FTC/TDF (N = 432)	EVG/COBI/FTC/TAF (N = 431)	EVG/COBI/FTC/TDF (N = 435)
N	FAS	435	432	431	435
	PP	[redacted]	[redacted]	[redacted]	[redacted]
HIV-1 RNA < 50 copies/mL, n (%)	FAS	405 (93.1)	399 (92.4)	395 (91.6)	385 (88.5)
	PP	[redacted]	[redacted]	[redacted]	[redacted]
Difference in % (95% CI);[b] *P* value	FAS	1.0 (–2.6 to 4.5); *P* = 0.58[c]		3.1 (–1.0 to 7.1); *P* = 0.13[c]	
	PP	[redacted]		[redacted]	
AEs					
Patients with > 0 AEs, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
SAEs					
Patients with > 0 SAEs, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
WDAEs					
WDAEs, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Deaths					
Number of deaths, n (%)		1 (0.2)	1 (0.2)	1 (0.2)	2 (0.5)

AE = adverse event; CI = confidence interval; COBI = cobicistat; EVG = elvitegravir; FAS = full analysis set; FTC = emtricitabine; PP = per-protocol; RNA = ribonucleic acid; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; WDAE = withdrawal due to adverse event.

[a] Non-inferiority margin is 12%.

[b] CI for studies 104 and 111 is 95.002%.

[c] Superiority test was conducted if non-inferiority was achieved.

Source: Clinical Study Reports from manufacturer (study 104[2] and study 111).[3]

TABLE 2: SUMMARY OF RESULTS — VIROLOGICALLY SUPPRESSED ADULTS (RANDOMIZED CONTROLLED TRIALS)

		Study 109		Study 1089	
		EVG/COBI/FTC/TAF (N = 959)	FTC/TDF + 3rd Drug (N = 477)	FTC/TAF + 3rd Drug (N = 333)	FTC/TDF + 3rd Drug (N = 330)
Virologic Success[a]					
N	FAS	959	477	333	330
	PP	921	440	304	305
HIV-1 RNA < 50 copies/mL, n (%)	FAS	932 (97.2)	444 (93.1)	314 (94.3)	307 (93.0)
	PP	913 (99.1)	435 (98.9)	[redacted]	[redacted]
Difference in % (95% CI);[b] *P* value	FAS	4.1 (1.6 to 6.7); *P* = 0.0002[c]		1.3 (–2.5 to 5.1); *P* = 0.5[c]	
	PP	0.3 (NR); *P* = NR		[redacted]	
AEs					
Patients with > 0 AEs, n (%)		828 (86.3)	399 (83.7)	281 (84.4)	262 (79.4)
SAEs					
Patients with > 0 SAEs, n (%)		65 (6.8)	35 (7.3)	18 (5.4)	14 (4.2)
WDAEs					
WDAEs, n (%)		9 (0.9)	12 (2.5)	7 (2.1)	3 (0.9)
Deaths					
Number of deaths, n (%)		4 (0.4)	0	1 (0.3)	0

AE = adverse event; CI = confidence interval; COBI = cobicistat; EVG = elvitegravir; FAS = full analysis set; FTC = emtricitabine; NR = not reported; PP = per-protocol; RNA = ribonucleic acid; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; WDAE = withdrawal due to adverse event.

[a] Non-inferiority margin is 12% for study 109, 10% for study 1089.

[b] CI for study 109 was 95.01%. For study 1089, it was 95.002%.

[c] Superiority test was conducted if non-inferiority was achieved.

Source: Clinical Study Reports from manufacturer (study 109 [6] and study 1089).[16]

TABLE 3: SUMMARY OF RESULTS — SPECIAL POPULATIONS (OPEN-LABEL, SINGLE-ARM)

	Study 112 (Reduced Kidney Function)				Study 106 (ART-Naive Adolescents)
	Switch to EVG/COBI/FTC/TAF			ART-Naive EVG/COBI/FTC/TAF (N = 6)	EVG/COBI/FTC/TAF (N = 48)
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $EGFR_{CG}$ ≥ 50 mL/Min (N = 162)	Total (N = 242)		
Virologic success					
N	80	162	242	6	23
HIV-1 RNA < 50 copies/mL, n (%)	76 (95.0)	154 (95.1)	230 (95.0)	5 (83.3)	21 (91.3)
AEs					
Patients with > 0 AEs, n (%)	67 (83.8)	142 (87.7)	209 (86.4)	5 (83.3)	39 (81.3)
SAEs					
Patients with > 0 SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	4 (8.3)
WDAEs					
WDAEs, n (%)	6 (7.5)	2 (1.2)	8 (3.3)	0	0
Deaths					
Number of deaths, n (%)	0	0	0	0	0

AE = adverse event; ART = antiretroviral therapy; COBI = cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FTC = emtricitabine; RNA = ribonucleic acid; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; WDAE = withdrawal due to adverse event.
Note: In studies 112 and 106, the interim analysis for virologic success included patients who have the last available HIV-1 RNA < 50 copies/mL in the week 24 analysis window while on treatment.
Source: Clinical Study Reports from manufacturer (study 112 [4] and study 106).[5]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

HIV attacks $CD4^+$ T cells, components of the immune system that are necessary for defending the body against infection.[17] HIV progressively impairs immune response and, if left untreated, may lead to acquired immunodeficiency syndrome (AIDS), the final stage of HIV where a patient can no longer fight off infections and certain malignancies. HIV is transmitted through bodily fluids, and can be passed from an infected individual to a healthy individual through unprotected sex and sharing of drug needles.[18] An infected mother can also pass the virus to her baby during pregnancy, birth, or through breastfeeding (vertical transmission). HIV can be divided into two major types: HIV type 1 (HIV-1) and HIV type 2 (HIV-2), between which HIV-1 is the predominant virus worldwide. [19]

At the end of 2014, Health Canada estimated that 75,500 people were living with HIV infection in Canada,[20] an increase of 6,700 (9.7%) from 2011. Men who have sex with men accounted for 53% of the total; injection-drug users 19%; heterosexuals 31%, likely through blood transfusions or clotting factors; and transmission from mother to child, or needle-stick injuries, less than 1%.[20]

In 2011, approximately 95% of reported HIV/AIDS cases were from Ontario (42.6%), Quebec (21.5%), British Columbia (13.4%), Alberta (9.7%), and Saskatchewan (7.7%).[21] The incidence in Canada of HIV infection was estimated at 3,175 (range: 2,250 to 4,100) cases in 2011, which was similar to data from 2008.[21] Regional estimates are not yet available for 2014.[20]

1.2 Standards of Therapy

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 (VL), which leads to restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.[22]

The choice of the optimal antiretroviral treatment (ART) for an individual patient must take into account drug potency, tolerability, convenience, patient treatment adherence, and known or potential drug interactions, as well as patient comorbidities, ART history, concomitant medication use, and cost. According to the clinical expert involved in this review, single-tablet regimens are the preferred therapy for the majority of patients given their convenience. However, for patients who have viral resistance, comorbidities, or drug interactions, a multi-tablet regimen may be indicated.

As viral mutations conferring resistance to ART can occur only during viral replication, the goal of ART is the complete suppression of viral replication, as determined by repeated VL measurements below assay limit.[23] Virologic failure occurs when viral suppression is not achieved or maintained. A number of published guidelines are available to assist clinicians in choosing an appropriate first-line therapy. According to the consulting clinical expert for this review, the guidelines published by the US Department of Health and Human Services (DHHS) are the most commonly used in Canada.[22] In the DHHS guidelines (2016), one single-tablet regimen containing emtricitabine/tenofovir alafenamide fumarate (FTC/TAF) (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate [EVG/COBI/FTC/TAF], Genvoya) is listed as one of the recommended initial regimens for ART-naive adults and adolescents with estimated creatinine clearance ≥ 30 mL/min.[22] EVG/COBI/FTC/TAF was approved by Health Canada in November 2015 [24] (Table 4), and received a positive CADTH Canadian Drug Expert Committee (CDEC) recommendation in February 2016.[25] TAF plus lamivudine (3TC) or TAF

plus FTC were recommended to be used in adolescents aged ≥ 12 years and not sexually mature (Sexual Maturity Rating [Tanner Staging] I to III) in the DHHS pediatric HIV treatment guidelines (2016)[9] (Table 5).

Treatment-Naive Adults
The DHHS recommends six regimens for ART-naive patients: five integrase strand-transfer inhibitor (INSTI)-based regimens and one ritonavir-boosted protease inhibitor (PI/r)-based regimen, as follows:

INSTI-based regimens:
- Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) — only for patients who are HLA-B*5701 negative
- Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) + DTG
- EVG/COBI/TAF/FTC — only for patients with pre-ART creatinine clearance (CrCl) ≥ 30 mL/min
- EVG/COBI/TDF/FTC — only for patients with pre-ART CrCl ≥70 mL/min
- TDF/FTC + raltegravir (RAL)

PI/r-based regimen:
- TDF/FTC + ritonavir-boosted darunavir (DRV/r)

In Canada, three of the above-mentioned preferred regimens are available as single-tablet regimens: Genvoya (EVG/COBI/FTC/TAF), Stribild (EVG/COBI/FTC/TDF), and Triumeq (DTG/ABC/3TC). The three remaining preferred regimens are available as multi-tablet regimens consisting of a two-drug backbone, TDF/FTC (Truvada) + a third drug. There are two additional single-tablet regimens available, although they are listed as “alternative” by the DHHS, as follows: Atripla (efavirenz [EFV]/TDF/FTC) and Complera (rilpivirine [RPV]/TDF/FTC). Key characteristics of these regimens are presented in Table 4.

TABLE 4: KEY CHARACTERISTICS OF US DEPARTMENT OF HEALTH AND HUMAN SERVICES–RECOMMENDED HIV REGIMENS FOR ANTIRETROVIRAL THERAPY–NAIVE PATIENTS AVAILABLE IN CANADA

	Truvada + 3rd ARV Drug	Genvoya	Stribild	Triumeq	Atripla	Complera
DHHS Listing	Recommended backbone for other multiple-tablet ART regimens[a]	Recommended	Recommended	Recommended	Alternative	Alternative
Base	INSTI or PI/r	INSTI	INSTI	INSTI	NNRTI	NNRTI
Regimen	FTC/TDF + DTG; FTC/TDF + RAL; FTC/TDF + DRV/r	EVG/COBI/FTC/TAF	EVG/COBI/FTC/TDF	DTG/ABC/3TC	EFV/TDF/FTC	RPV/FTC/TDF
Mechanism of Action	**N(t)RTI** (e.g., TDF, FTC), **NNRTI** (e.g., EFV): inhibits HIV reverse transcriptase to prevent early-cycle viral replication; **INSTI** (e.g., RAL): inhibits HIV integrase to prevent entry of viral DNA into host cell genome					
Indication[b]	In combination with other ARV drugs for the treatment of HIV-1 infection in adults	As a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older (and weighing ≥ 35 kg)	As a complete regimen for the treatment of adults aged 18 years and older infected with HIV-1 with no known mutations to the integrase inhibitor class, tenofovir or emtricitabine	For the treatment of HIV infection in adults	For the treatment of HIV-1 infection in adults	For the treatment of HIV-1 infection in ART-naive adults
Route of Administration	Oral					
Recommended Dose	FTC 200 mg/TDF 300 mg once daily	EVG 150 mg/COBI 150 mg/FTC 200 mg /TAF 10 mg once daily	EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg once daily	DTG 50 mg/ ABC 600 mg/3TC 300 mg once daily	EFV 600 mg/ TDF 300 mg/ FTC 200 mg once daily	FTC 200 mg/ RPV 25 mg/ TDF 300 mg once daily
Serious Side Effects/ Safety Issues	**Contraindications:** Patients with previously demonstrated hypersensitivity to	**Contraindications:** Patients with known hypersensitivity to any of the components	**Contraindications:** Patients with previously demonstrated hypersensitivity to	**Contraindications:** Patients who are hypersensitive to this drug or to any ingredient in the	**Contraindications:** Patients with previously demonstrated hypersensitivity to	**Contraindications:** Patients with previously demonstrated hypersensitivity to

	Truvada + 3rd ARV Drug	Genvoya	Stribild	Triumeq	Atripla	Complera
	any of the components of the product **Warnings and precautions:** – Lactic acidosis and severe hepatomegaly with steatosis; – patients coinfected with HBV and HIV	of the product **Warnings and precautions:** – Lactic acidosis and severe hepatomegaly with steatosis; – Post-treatment exacerbation of hepatitis	any of the components of product; multiple drugs **Warnings and precautions:** Lactic acidosis and severe hepatomegaly with steatosis; post-treatment exacerbations of HBV; nephrotoxicity	formulation or component of the container; patients who are positive for the HLA-B*5701 allele and patients with a prior history of a hypersensitivity reaction to ABC, or products containing ABC, regardless of HLA-B*5701 status; patients who are prescribed dofetilide **Warnings and precautions:** Fatal hypersensitivity reactions; lactic acidosis and severe hepatomegaly with steatosis; post-treatment exacerbations of hepatitis B	any of the components of product; multiple drugs **Warnings and precautions:** Lactic acidosis; severe hepatomegaly with steatosis; safety and efficacy not established in patients coinfected with HBV and HIV; kidney failure, renal insufficiency, elevated creatinine, hypophosphatemia, and Fanconi syndrome have been reported with the use of TDF	FTC, RPV, TDF, or to any of the excipients; multiple drugs **Warnings and precautions:** Lactic acidosis; severe hepatomegaly with steatosis; safety and efficacy not established in patients coinfected with HBV and HIV; renal insufficiency, elevated creatinine, hypophosphatemia, and Fanconi syndrome have been reported with the use of TDF

3TC = lamivudine; ABC = abacavir; ART = antiretroviral treatment; COBI = cobicistat; DRV/r = ritonavir-boosted darunavir; DNA = deoxyribonucleic acid; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand-transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; N(t)RTI = nucleos(t)ide analogue reverse transcriptase inhibitor; PI/r = ritonavir-boosted protease inhibitor; r =ritonavir; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

[a] Health Canada indication.

Source: Product monographs for Truvada,[26] Genvoya,[24] Stribild,[27] Triumeq,[28] Atripla,[29] and Complera.[30]

Treatment-Experienced Adults

Apart from virologic failure, changes to ART may be necessary due to adverse events (AEs). Because of the large number of drug options available, careful single or multiple substitution of the components of an anitretroviral (ARV) regimen can continue to offer optimal virologic suppression with improved tolerability or adherence.

The DHHS does not make specific recommendations for the treatment of ART-experienced patients. Rather, it recommends that a new regimen should include at least two, and preferably three, fully active drugs, which it defines as those that are expected to have "uncompromised activity on the basis of the patient's treatment history and drug-resistance testing results and/or the drug's novel mechanism of action."[22]

However, the DHHS notes that before modifying a regimen, it is critical to carefully evaluate the cause(s) of virologic failure, including incomplete adherence, poor tolerability, and drug and food interactions, and to review HIV ribonucleic acid (RNA) and CD4 cell count changes over time, as well as treatment history and drug-resistance test results. If HIV RNA suppression is not possible with currently approved drugs, it suggests use of investigational drugs; failing that, the choice of regimens should focus on minimizing toxicity and preserving treatment options while maintaining CD4 cell counts to delay clinical progression.

Adolescents

The DHHS recommends that the dosage of medications for HIV infection should be prescribed according to the Tanner staging of puberty and not exclusively by age.[9] In particular, it suggests that adolescents in early puberty (i.e., Tanner Stages I and II) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult schedules. Nevertheless, the DHHS emphasizes that selection of an initial regimen should be based on the characteristics of the proposed regimen, patient characteristics, and viral resistance test results.

Among children aged 12 years and older, the DHHS recommends abacavir plus lamivudine (ABC + 3TC) or ABC + FTC as the nucleos(t)ide analogue reverse transcriptase inhibitor (N(t)RTI) backbone. A list of the DHHS-recommended alternative and acceptable regimens most relevant to the population under consideration for this review is presented in Table 5.

TABLE 5: US DEPARTMENT OF HEALTH AND HUMAN SERVICES–RECOMMENDED REGIMENS FOR INITIAL THERAPY OF HIV INFECTION IN CHILDREN AND ADOLESCENTS

Preferred Regimens	
Adolescents aged ≥ 12 years and not sexually mature (SMR I to III)	2 NRTIs plus ATV/r
	2 NRTIs plus DTG[a]
	2 NRTIs plus once daily DRV/r[b]
	2 NRTIs plus EVG/c[c]
Adolescents aged ≥ 12 years and sexually mature (SMR IV or V)	Refer to *Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents* [22]
Alternative Regimens	
Adolescents aged ≥ 12 years and not sexually mature (SMR I to III)	2 NRTIs plus EFV[d]
	2 NRTIs plus RAL[e]
	2 NRTIs plus RPV[f]
Preferred 2-NRTI Backbone Options for Use in Combination With Additional Drugs	
Adolescents aged ≥ 12 years and not sexually mature (SMR I to III)	ABC plus (3TC or FTC)
	TAF plus (3TC or FTC)
Adolescents aged ≥ 12 years and sexually mature (SMR IV or V)	Refer to *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* [22]
Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Adolescents at SMR III	TDF plus (3TC or FTC)
Adolescents aged ≥ 12 Years at SMR III	ZDV plus (3TC or FTC)
2-NRTI Regimens for Use in Special Circumstances in Combination with Additional Drugs	
Children aged ≥ 2 years and adolescents, SMR I or II	TDF plus (3TC or FTC)

3TC = lamivudine; ABC = abacavir; ATV/r = ritonavir-boosted atazanavir; COBI = cobicistat; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RPV = rilpivirine; SMR = Tanner Sexual Maturity Rating; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; VL = viral load; ZDV = zidovudine.
[a] DTG is recommended only for those adolescents aged ≥ 12 years and weighing ≥ 40 kg.
[b] DRV once daily should not be used in children aged < 12 years and if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
[c] EVG is currently recommended only in fixed-dose combination tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as preferred for children aged ≥ 12 years and weighing ≥ 35 kg. Tablets containing EVG/COBI/FTC/TDF are recommended only for adolescents aged ≥ 12 years, weighing ≥ 35 kg, and in SMR IV or V.
[d] EFV is licensed for use in children aged ≥ 3 months who weigh ≥ 3.5 kg, but is not recommended by the panel as initial therapy in children aged ≥ 3 months to 3 years. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.
[e] RAL pills or chewable tablets can be used in children aged ≥ 2 years. Granules can be administered in infants and children aged 4 weeks to 2 years.
[f] RPV should be administered to adolescents aged ≥ 12 years and weighing ≥ 35 kg who have an initial VL ≤ 100,000 copies/mL.
Source: US Department of Health and Human Services pediatric guideline 2016.[9]

1.2.1 Drug

FTC/TAF has a proposed Health Canada indication for use in combination with other ARVs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older (and weighing ≥ 35 kg). FTC/TAF is a single-tablet, two-drug, nucleoside reverse transcriptase inhibitor backbone fixed-dose combination that consists of FTC 200 mg, and TAF 10 mg and 25 mg. The 10 mg dose of TAF is recommended when FTC/TAF is used in combination with an HIV-1 PI that is boosted with either ritonavir or COBI; otherwise, the recommended dose of TAF is 25 mg.

TAF is a prodrug of tenofovir that undergoes intracellular activation by cathepsin A. Due to its increased plasma stability, TAF is proposed to be more efficient than TDF in loading tenofovir into peripheral blood mononuclear cells. The lower plasma concentrations of tenofovir, with TAF at therapeutic doses, minimize the unwanted "off-target" effects typically associated with TDF administration.

At the time of this review, FTC/TAF was under review by Health Canada, and was approved by the FDA in April 2016.[31] The FDA's indication for FTC/TAF is in combination with other ARV drugs for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.[32] FTC/TAF has not yet been approved by the European Medicines Agency, National Institute for Health Care and Excellence, PHARMAC, or HAS. A Marketing Authorization Application in the European Union for FTC/TAF was fully validated on May 28, 2015.[33]

FTC/TAF includes the components of FTC/TDF (Truvada), except that TDF in Truvada has been replaced with TAF. FTC/TDF was recommended for reimbursement by CDEC in December 2008 as an alternative for the initial phase of treatment of adult patients with HIV infection who have experienced intolerance or AEs with other nucleoside combinations, including 3TC in combination with zidovudine, ABC, stavudine or didanosine, and who have not developed virologic failure or clinical progression on initial ART. [1]

As per DHHS guidelines, the single-tablet regimen containing FTC/TAF (EVG/COBI/FTC/TAF) is one of the recommended initial regimens for ART-naive adults and adolescents with estimated CrCl ≥ 30 mL/min.[22] EVG/COBI/FTC/TAF was recommended for reimbursement by CDEC in March, 2016 as a complete regimen for the treatment of HIV type 1 infection in adult and pediatric patients 12 years of age and older with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF.[34]

Indication under review
In combination with other antiretrovirals (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older (and weighing ≥35 kg).
Reimbursement criteria requested by sponsor
For use in combination with other antiretrovirals for treatment of treatment-naive and virologically-suppressed HIV-1 infected adult and pediatric patients 12 years of age and older.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of FTC/TAF in combination with other ARVs (such as NNRTIs or PIs) for the treatment of HIV type 1 infection in adult and pediatric patients aged 12 years and older (weighing ≥ 35 kg).

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Studies were selected for inclusion based on the selection criteria presented in Table 6.

TABLE 6: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult and pediatric patients 12 years of age and older (weighing ≥ 35 kg) who are infected with immunodeficiency virus type 1 (HIV-1) Subgroups: • Baseline VL (> 100,000 versus ≤ 100,000 copies/mL) • Age (12 to 17 years versus ≥ 18 years) • eGFR (author-specified cut-off)	
Intervention	FTC/TAF (200 mg/10 mg or 200 mg/25 mg once daily)[a] in combination with other antiretrovirals	
	Standard of care; i.e., any of the following regimens in co-formulation or co-administered individually at the recommended doses:	
Comparators	• DTG/ABC/3TC • DTG + TDF/FTC • EVG/COBI/FTC/TAF • EVG/COBI/FTC/TDF	• RAL + TDF/FTC • DRV/r + TDF/FTC • DRV/c + TDF/FTC[b]
Outcomes	**Key efficacy outcome:** • Virologic success: percentage of patients with VL < 50 copies/mL (FDA-defined snapshot algorithm) (author-specified primary time point and longest time point) **Other outcomes:** • Resistance • Health-related quality of life[c] • Adherence[c] **Harms outcomes:** • SAEs • AEs • WDAEs • Notable harms (renal and bone systems)	
Study Design	Published and unpublished phase 3 RCTs	

3TC = lamivudine; ABC = abacavir; AE = adverse event; CDR = CADTH Common Drug Review; COBI = cobicistat; DTG = dolutegravir; DRV/c = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; eGFR = estimated glomerular filtration rate; EVG = elvitegravir; FTC = emtricitabine; RAL = raltegravir; RCT = randomized controlled trial; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; VL = viral load; WDAE = withdrawal due to adverse event.

[a] The 200 mg/10 mg dose is recommended when FTC/TAF is used in combination with an HIV-1 protease inhibitor that is boosted by either ritonavir or cobicistat; otherwise, the recommended dose of FTC/TAF is 200 mg/25 mg.

[b] CDR reviewers recognize that this regimen is listed as an alternative treatment regimen by the US Department of Health and Human Services' Panel on Antiretroviral Guidelines for Adults and Adolescents. This regimen was identified as a relevant comparator in consultation with the clinical expert involved in this review.

[c] Identified as an important outcome in the patient input submission to CDR.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were emtricitabine and tenofovir alafenamide.

No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on February 29, 2016. Regular alerts were established to update the search until the CDEC meeting on July 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials, and databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 7, Table 8, and Table 9; excluded studies (with reasons) are presented in Appendix 3APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of six studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in section 3.2. A list of excluded studies is presented in Appendix 3APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

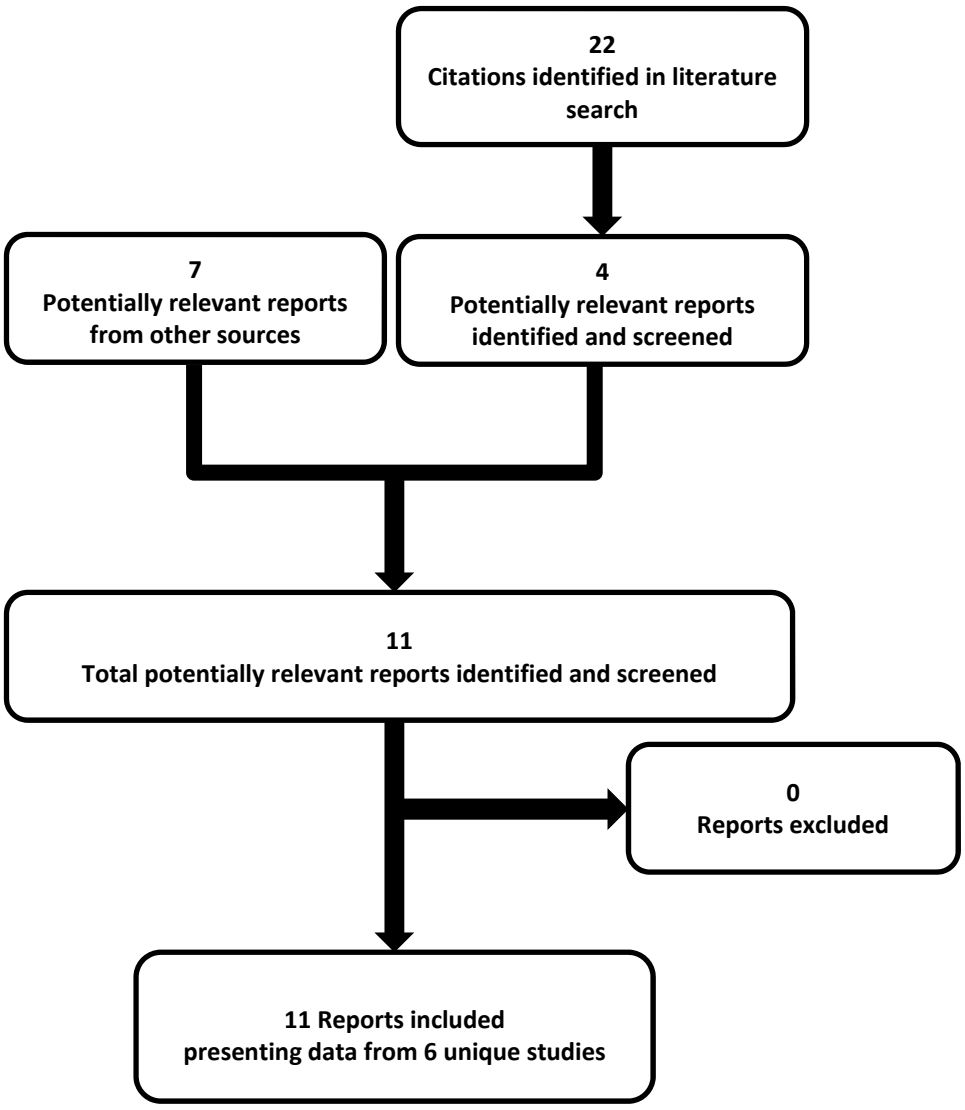

TABLE 7: DETAILS OF INCLUDED STUDIES — TREATMENT-NAIVE ADULTS (RANDOMIZED CONTROLLED TRIALS)

		Study 104	Study 111
DESIGNS & POPULATIONS	**Study Design**	Multi-centre, double-blind, double-dummy, active-controlled phase 3 non-inferiority RCT stratified by HIV-1 RNA VL, CD4 count, and region at screening	
	Locations	United States, Spain, Canada, Thailand, Australia, Switzerland, Austria, Belgium, Italy, Japan, United Kingdom	United States, United Kingdom, France, Canada, Italy, Portugal, Mexico, Netherlands, Sweden, Dominican Republic
	Randomized (N)	872	872
	Inclusion Criteria	Age ≥ 18 years; normal ECG; $eGFR_{CG}$ ≥ 50 mL/min; ALT and AST < 5 × ULN; total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin; ANC ≥ 1,000/mm^3, platelets ≥ 50,000/mm^3, Hb ≥ 8.5 g/L; serum amylase ≤ 5 × ULN (or > 5 × ULN with serum lipase ≤ 5 × ULN); using highly effective contraception methods if sexually active; HIV-1 RNA VL ≥ 1,000 copies/mL; ART-naive excluding use for PrEP or PEP up to 6 months prior to screening; screening HIV-1 genotype sensitive to EVG, FTC, TDF	
	Exclusion Criteria	New AIDS-defining condition < 30 days prior to screening; hepatitis B surface antigen positive; hepatitis C antibody positive; decompensated cirrhosis; pregnancy or breastfeeding; implanted defibrillator or pacemaker; current alcohol or substance use; malignancy (current or within past 5 years) other than KS, BCC, or resected, noninvasive CSC; active, serious (non-HIV) infection requiring parenteral AB or AF treatment; taking interacting drugs (according to list) or allergic to excipients of study drugs	
DRUGS	**Intervention**	FDC tablet of EVG/COBI/FTC/TAF (150 mg/150 mg/200 mg/10 mg) + placebo-to-match EVG/COBI/FTC/TDF once daily	
	Comparator(s)	FDC tablet of EVG/COBI/FTC/TDF (150 mg/150 mg/200 mg/300 mg) + placebo-to-match EVG/COBI/FTC/TAF once daily	
DURATION	**Phase**		
	Double-blind	96 weeks	
	Open-label	NA	
	Follow-up	Every 12 weeks following week 96 until treatment assignments were unblinded, at which point patients were given the option to participate in an OL rollover study to receive EVG/COBI/FTC/TAF	
OUTCOMES	**Primary End Point**	Virologic success (percentage of patients with HIV-1 RNA < 50 copies/mL) at week 48 (snapshot analysis)	
	Other End Points	Virologic success (percentage of patients with HIV-1 RNA < 50 copies/mL) at week 96 (snapshot analysis); resistance; EQ-5D-3L	
NOTES	**Publications**	Sax et al.[35] Wohl et al.[36]	

AB = antibiotic; AF = antifungal; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ART = antiretroviral therapy; AST = aspartate aminotransferase; BCC = basal cell carcinoma; COBI = cobicistat; CSC = cutaneous squamous carcinoma; ECG = electrocardiogram; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire, 3 Levels; EVG = elvitegravir; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; FDC = fixed-dose combination; FTC = emtricitabine; Hb = hemoglobin; KS = Kaposi sarcoma; NA = not applicable; OL = open-label; PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis; RCT = randomized controlled trial; RNA = ribonucleic acid; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal; VL = viral load.
Source: Clinical Study Reports, studies 104[2] and 111.[3]

TABLE 8: DETAILS OF INCLUDED STUDIES — VIROLOGICALLY SUPPRESSED ADULTS (RANDOMIZED CONTROLLED TRIALS)

		Study 109	Study 1089
DESIGNS & POPULATIONS	**Study Design**	Multi-centre, open-label, active-controlled phase 3 non-inferiority RCT stratified by prior treatment regimen at screening.	Multi-centre, DB, active-controlled phase 3 non-inferiority RCT stratified by prior treatment regimen at screening.
	Locations	Australia, Austria, Belgium, Brazil, Canada, Denmark, Dominican Republic, France, Germany, Italy, Mexico, Netherlands, Portugal, Spain, Sweden, Switzerland, Thailand, United Kingdom, Puerto Rico, United States	Belgium, Canada, France, Italy, United Kingdom, United States
	Randomized (N)	1,443	668
	Inclusion Criteria	Age ≥ 18 years; normal ECG; $eGFR_{CG}$ ≥ 50 mL/min; ALT and AST < 5 × ULN; total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin; ANC ≥ 1,000/mm^3, platelets ≥ 50,000/mm^3, Hb ≥ 8.5 g/L; serum amylase ≤ 5 × ULN (or > 5 × ULN with serum lipase ≤ 5 × ULN); using highly effective contraception methods if sexually active; on an ARV regimen consisting of FTC/TDF + 3rd drug for 6 consecutive months preceding the final visit in their earlier study; plasma HIV-1 RNA concentrations at undetectable levels for ≥ 6 consecutive months prior to screening and HIV RNA < 50 copies/mL at screening	
	Exclusion Criteria	New AIDS-defining condition < 30 days prior to screening; hepatitis B surface antigen positive; hepatitis C antibody positive; decompensated cirrhosis; pregnancy or breastfeeding; implanted defibrillator or pacemaker; current alcohol or substance use; malignancy (current or within past 5 years) other than KS, BCC, or resected, noninvasive CSC; active, serious (non-HIV) infection requiring parenteral AB or AF treatment; taking interacting drugs (according to list) or allergic to excipients of study drugs	
DRUGS	**Intervention**	Switch to EVG/COBI/FTC/TAF (150 mg/150 mg/200 mg/10 mg)	FTC/TAF + placebo-to-match FTC/TDF + 3rd ARV drug (The 3rd drug remains the same. TAF dose of 10 mg or 25 mg was administered based on the general recommendation that FTC/TAF 200 mg/25 mg should be used with unboosted third drugs and FTC/TAF 200 mg/10 mg should be used with boosted third drugs.)
	Comparator(s)	Stay on pre-existing FTC/TDF + 3rd drug regimen	FTC/TDF + placebo-to-match FTC/TAF + a 3rd ARV drug (the 3rd drug remains the same.)
DURATION	**Phase**		
	Double-blind	NA	48 weeks[a]
	Open-label	48 weeks[a]	NA
	Follow-up	Every 12 weeks following week 96, at which point patients were given the option to receive OL EVG/COBI/FTC/TAF	NA

		Study 109	Study 1089
Outcomes	**Primary End Point**	Virologic success (percentage of patients with HIV-1 RNA < 50 copies/mL) at week 48 (snapshot analysis)	Virologic success (percentage of patients with HIV-1 RNA < 50 copies/mL) at week 48 (snapshot analysis)
	Other End Points	Resistance; EQ-5D-3L; SF-36	Resistance
Notes	**Publications**	Mills et al., 2016 [37]	Gallant et al., 2016[38]

AB = antibiotic; AF = antifungal; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ARV = antiretroviral; AST = aspartate aminotransferase; ATV/r = ritonavir-boosted atazanavir; BCC = basal cell carcinoma; COBI = cobicistat; CSC = cutaneous squamous carcinoma; DB = double-blind; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire, 3 Levels; ECG = electrocardiogram; EVG = elvitegravir; eGFRCG = estimated glomerular filtration rate according to the Cockcroft–Gault formula; FTC = emtricitabine; Hb = hemoglobin; KS = Kaposi sarcoma; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NA = not applicable; NVP = nevirapine; OL = open-label; RAL = raltegravir; RCT = randomized controlled trial; RNA = ribonucleic acid; RPV = rilpivirine; SF-36 = Short Form 36 Health Survey; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal.

[a] Studies 109 and 1089 were designed for 96 weeks. However, the data presented in this review for both studies were from the interim and final 48-week analyses.

Note: Third drug included ATV/r, LPV/r, DRV/r, EFV, RPV, NVP, RAL, DTG, MVC in study 1089.

Source: Clinical Study Report, studies 109[6] and 1089.[16]

TABLE 9: DETAILS OF INCLUDED STUDIES — SPECIAL POPULATIONS (OPEN-LABEL SINGLE-ARM)

		Study 112 (Reduced Kidney Function, Mainly Virologically Suppressed Adults)	Study 106 (Treatment-Naive Adolescents)
Designs & Populations	**Study Design**	Multi-centre, open-label, phase 3 single-arm interventional study	Multi-centre, open-label, phase 2/3, multipart single-arm interventional study
	Locations	United States, Thailand, United Kingdom, Australia, Spain, France, Dominican Republic, Mexico, Netherlands	Thailand, United States, South Africa, Uganda
	Enrolled (N)	252	48 (24 in Part A, 24 in Part B)
	Inclusion Criteria	All cohorts: Age ≥ 18 years; CD4+ count ≥ 50 cells/µL; stable kidney function; cause of underlying chronic kidney disease stable; normal ECG; ALT and AST < 5 × ULN; total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin; ANC ≥ 1,000/mm^3, platelets ≥ 50,000/mm^3, Hb ≥ 8.5 g/L; serum amylase ≤ 5 × ULN (or > 5 × ULN with serum lipase ≤ 5 × ULN); using highly effective contraception methods if sexually active	Age 12 to 18 years; weight ≥ 35 kg; HIV-1 RNA VL ≥ 1,000 copies/mL; CD4+ count > 100 cells/µL; screening genotype sensitive to EVG, FTC, and TFV; adequate renal function: eGFR (using Schwartz formula) ≥ 90 mL/min/1.73 m^2; normal ECG; documented screening for active pulmonary tuberculosis within 6 months screening; ALT and AST < 5 × ULN; total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin; ANC ≥ 1,000/mm^3, platelets ≥ 50,000/mm^3, Hb ≥ 8.5 g/L; no prior use of any approved or experimental anti–HIV-1 drug for any length of time; using

		Study 112 (Reduced Kidney Function, Mainly Virologically Suppressed Adults)	Study 106 (Treatment-Naive Adolescents)
		Cohort 1: Virologically suppressed patients, no known resistance to EVG, TDF, or FTC; plasma HIV-1 RNA undetectable for ≥ 6 consecutive months prior to screening and HIV-1 RNA VL < 50 copies/mL at screening; $eGFR_{CG}$ 30 mL/min to 69 mL/min using actual weight Cohort 2: Treatment-naive patients, HIV-1 RNA VL ≥ 1,000 copies/mL; screening HIV-1 genotype sensitive to EVG, FTC, TDF; ART-naive excluding use for PrEP or PEP up to 6 months prior to screening; $eGFR_{CG}$ 30 mL/min to 69 mL/min using actual weight	highly effective contraception methods if sexually active; life expectancy > 1 year
	Exclusion Criteria	New AIDS-defining condition < 30 days prior to screening; hepatitis B surface antigen positive; hepatitis C antibody positive; receiving or anticipated to receive drug treatment for hepatitis C; decompensated cirrhosis; pregnancy or breastfeeding; implanted defibrillator or pacemaker; current alcohol or substance use; malignancy (current or within past 5 years) other than KS, BCC, or resected, noninvasive CSC; active, serious (non-HIV) infection requiring parenteral AB or AF treatment; patients on hemodialysis, other forms of renal replacement therapy, or on treatment for underlying kidney diseases; taking interacting drugs (according to list) or allergic to excipients of study drugs	New AIDS-defining condition < 30 days prior to screening; hepatitis B surface antigen positive; hepatitis C antibody positive; prior treatment with any approved or investigational or experimental anti–HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission); evidence of active pulmonary or extrapulmonary tuberculosis disease within 3 months of screening; anticipated to require rifamycin treatment for mycobacterial infection while participating in study; decompensated cirrhosis; pregnancy or breastfeeding; implanted defibrillator or pacemaker; active or serious medical or psychiatric illness that, per the investigator's opinion, would interfere with treatment assessment or compliance; current alcohol or substance use; history of significant drug sensitivity or drug allergy; known hypersensitivity to study drugs, metabolites, or formulation excipients; treatment with immunosuppressant therapies or chemotherapeutic drugs within 3 months of screening or expected to receive these drugs during study; malignancy (current or within past 5 years) other than KS, BCC, or resected, noninvasive CSC; active, serious (non-HIV) infection requiring parenteral AB or AF treatment; taking interacting drugs (according to list) or allergic to excipients of study drugs
DRUGS	**Intervention**	EVG/COBI/FTC/TAF (150 mg/150 mg/200 mg/10 mg)	

		Study 112 (Reduced Kidney Function, Mainly Virologically Suppressed Adults)	Study 106 (Treatment-Naive Adolescents)
DURATION	**Phase**		
	Open-label	96 weeks	Part A: 48 weeks (to evaluate steady-state PK and confirm the dose of EVG/COBI/FTC/TAF); Part B: 48 weeks (to evaluate the safety, tolerability, and antiviral activity of EVG/COBI/FTC/TAF)
	Follow-up	After week 96, patients continued to take their study drug and receive the EVG/COBI/FTC/TAF until it became commercially available, or until manufacturer terminated the development of EVG/COBI/FTC/TAF, with the exception of sites in Sweden. Patients who completed the study through week 96 and did not wish to continue to receive the study drug were required to return to the clinic 30 days after the completion of study drug for the 30-day follow-up visit.	Patients who completed 48 weeks on study treatment were given the option to participate in an extension phase of the study until: (a) the participant turned 18 and EVG/COBI/FTC/TAF was commercially available for adults in the country in which the participant was enrolled; (b) EVG/COBI/FTC/TAF became commercially available for adolescents in the country in which the participant was enrolled; or (c) manufacturer elected to terminate development of EVG/COBI/FTC/TAF in that country. Patients who completed the study through week 48 and did not wish to participate in the extension study were required to return to the clinic 30 days after completion of the week 48 visit for a follow-up visit.
OUTCOMES	**Primary End Point**	Virologic success (percentage of patients with HIV-1 RNA < 50 copies/mL) at week 24 (snapshot analysis)	
	Other End Points	Resistance	Resistance
NOTES	**Publications**	Pozniak et al., 2015[39]	None

AB = antibiotic; AF = antifungal; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ART = antiretroviral therapy; AST = aspartate aminotransferase; BCC = basal cell carcinoma; COBI = cobicistat; CSC=cutaneous squamous carcinoma; ECG = electrocardiogram; EVG = elvitegravir; eGFR = estimated glomerular filtration; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; FTC = emtricitabine; Hb = hemoglobin; KS = Kaposi sarcoma; PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis; RNA = ribonucleic acid; TAF = tenofovir alafenamide fumarate; TFV = tenofovir; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal; VL = viral load.

Source: Clinical Study Reports, studies 112[4] and 106.[5]

3.2 Included Studies

3.2.1 Description of Studies

The evidence for this review was drawn from six studies. Five of the six studies [2-6] were reviewed in the CDR submission for EVG/COBI/FTC/TAF (Genvoya). The inclusion of studies evaluating the FTC/TAF-based ART regimen EVG/COBI/FTC/TAF was based on evidence from two bioequivalence studies. These studies were randomized, open-label, single-dose, two-way crossover phase 1 studies (study 1472[7] and study 1473[8]) that evaluated the bioequivalence of FTC and TAF between a) FTC/TAF FDC + EVG + COBI[7] or b) FTC/TAF FDC,[8] and EVG/COBI/FTC/TAF. The FTC and TAF components of FTC/TAF + EVG + COBI,[7] or FTC/TAF FDC,[8] were found to be bioequivalent to the FTC and TAF components of EVG/COBI/FTC/TAF. The sixth study was not included in the CDR review of EVG/COBI/FTC/TAF. For a detailed summary of the bioequivalence studies, please see 0.

a) Studies in Treatment-Naive Adult Patients

Studies 104 [2] (n = 872) and 111 [3] (n = 872) were similarly designed multi-centre, double-blind, double-dummy, active-controlled, phase 3 non-inferiority trials. Randomization was stratified by VL (≤ 100,000, > 100,000 to ≤ 400,000, or > 400,000), CD4 count (< 50 cells, 50 to 199, or ≥ 200), and region (US versus non-US) at screening. Both studies enrolled ART-naive patients from North America and Europe; study 104 also enrolled patients from Australia and Asia, while study 111 additionally enrolled patients from Latin America. In both studies, the single-tablet co-formulation of EVG/COBI/FTC/TAF once daily was compared (1:1) against a once-daily, single-tablet co-formulation of EVG/COBI/FTC/TDF. Originally planned for 96 weeks, studies 104 and 111 were extended to 144 weeks; data from the studies presented in this systematic review are primarily from the interim 48-week analyses. The primary efficacy outcome was the percentage of patients with HIV RNA VL < 50 copies/mL at week 48.

b) Studies in Virologically Suppressed Adult Patients

Study 109 [6] (n = 1,443) was a multi-centre, open-label, active-controlled phase 3 non-inferiority trial. Randomization was stratified by prior treatment regimen at screening (0, Table 31). The study enrolled patients from North America, Europe, Australia, Asia, and Latin America. Patients on an ARV regimen consisting of FTC/TDF + a third ARV drug were randomized (2:1) to be switched to EVG/COBI/FTC/TAF or remain on their pre-existing regimen. Data for study 109 (originally planned for 96 weeks) presented in the systematic review are from the 48-week analyses. The primary efficacy outcome was the percentage of patients with HIV RNA VL < 50 copies/mL at week 48.

Study 1089 [16] (n = 668) was a multi-centre, double-blind, active-controlled phase 3 non-inferiority trial. Randomization was stratified by prior treatment regimen at screening (0, Table 31). The study enrolled patients from North America and Europe. Patients on an ARV regimen consisting of FTC/TDF + a third drug were randomized (1:1) to be switched to FTC/TAF + the same third drug or remain on their pre-existing regimen (FTC/TDF + a third agent). Data for study 1089 (originally planned for 96 weeks) presented in the systematic review are from the interim 48-week analyses. In this study, the primary efficacy outcome was the percentage of patients with HIV RNA VL < 50 copies/mL at week 48.

c) Studies in Patients With Reduced Kidney function and in Adolescent (≥ 12 Years Old) Patients

Studies 112[4] (n = 252) and 106 [5] (n = 48) were multi-centre, open-label cohort studies that tested the efficacy and safety of EVG/COBI/FTC/TAF in patients with reduced kidney function and in adolescent (≥ 12 years old) patients, respectively. The total duration of study 112 was 96 weeks, whereas study 106 comprised two parts, each of which was 48 weeks in duration: in part A, the steady-state pharmacokinetic (PK) was evaluated and the dose of EVG/COBI/FTC/TAF was confirmed, while in part B,

the safety, tolerability, and antiviral activity of EVG/COBI/FTC/TAF were evaluated. In both studies, the primary efficacy outcome was the percentage of patients with HIV RNA VL < 50 copies/mL at week 24.

3.2.2 Populations

a) Inclusion and exclusion criteria

Studies 104 and 111 had the same inclusion and exclusion criteria. Both studies exclusively enrolled treatment-naive adults (≥ 18 years). Study 109 exclusively enrolled virologically suppressed adults who had been on one of four ART regimens consisting of FTC/TDF + a third drug: EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/COBI + FTC/TDF, or ritonavir-boosted atazanavir (ATV/r) + FTC/TDF. Similarly to study 109, study 1089 exclusively enrolled virologically suppressed adults who had been on FTC/TDF + one of the following ARV drugs: ATV/r, lopinavir boosted with ritonavir (LPV/r), darunavir boosted with ritonavir (DRV/r), efavirenz (EFV), rilpivirine (RPV), nevirapine (NVP), raltegravir (RAL), dolutegravir (DTG), and maraviroc (MVC) (0, Table 31).

Study 112 largely enrolled virologically suppressed adults (n = 246; 97.6%) who switched to EVG/COBI/FTC/TAF from their existing ART regimen. The remainder of patients were treatment-naive adults (n = 6; 2.4%). All patients had mild to moderate kidney impairment (estimated glomerular filtration rate according to the Cockcroft–Gault formula [$eGFR_{CG}$] of 30 mL/min to 69 mL/min). Study 106 exclusively enrolled treatment-naive adolescents (12 to 18 years of age).

b) Baseline Characteristics

Across the five studies that exclusively enrolled adults (studies 104, 111, 109, 112, and 1089), patients were predominantly male and white. The mean age of patients enrolled in studies 104, 111, 109, and 1089 ranged from 35 to 48 years; in study 112, the mean age was over 50 years. Patient body mass index (BMI) appeared to be similar across all five studies, and most patients were considered to have asymptomatic HIV. Across the five adult-only studies, the most common HIV risk factor category was homosexual sex. In study 106, which exclusively enrolled adolescents, the most common HIV risk factor was vertical transmission. Apart from study 112, which enrolled patients with reduced kidney function, patients in all studies generally appeared to have normal kidney function with estimated mean GFRs over 100 units, calculated either by the Cockcroft–Gault formula for those aged 18 years and older (mL/min) or the Schwartz formula (original) for those younger than 18 years (mL/min/1.73m^2) (Table 10, Table 11, and Table 12).

TABLE 10: SUMMARY OF BASELINE CHARACTERISTICS — TREATMENT-NAIVE ADULTS (RANDOMIZED CONTROLLED TRIALS)

Characteristic	Study 104		Study 111	
	EVG/COBI/FTC/TAF (N = 435)	EVG/COBI/FTC/TDF (N = 432)	EVG/COBI/FTC/TAF (N = 431)	EVG/COBI/FTC/TDF (N = 435)
Age (y)				
Mean (SD)	35 (10.0)	36 (10.5)	35 (10.8)	36 (10.9)
Median	33	35	33	34
Min, max	18, 74	18, 76	18, 66	18, 71
Sex, n (%)				
Male	364 (83.7)	376 (87.0)	369 (85.6)	364 (83.7)
Race, n (%)				
White	250 (57.5)	255 (59.0)	235 (54.5)	243 (55.9)
Black	94 (21.6)	81 (18.8)	129 (29.9)	132 (30.3)
Asian	76 (17.5)	77 (17.8)	15 (3.5)	12 (2.8)

Characteristic	Study 104		Study 111	
	EVG/COBI/FTC/TAF (N = 435)	EVG/COBI/FTC/TDF (N = 432)	EVG/COBI/FTC/TAF (N = 431)	EVG/COBI/FTC/TDF (N = 435)
Other	15 (3.5)	19 (4.4)	52 (12.1)	48 (11.0)
BMI (kg/m^2)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
HIV-1 RNA (log_{10} copies/mL) at baseline				
Mean (SD)	4.55 (0.68)	4.55 (0.67)	4.53 (0.65)	4.50 (0.69)
HIV-1 RNA category (copies/mL), n (%)				
< 50	NR	NR	NR	NR
≥ 50	NR	NR	NR	NR
≤ 100,000	331 (76.1)	336 (77.8)	339 (78.7)	336 (77.2)
> 100,000 to ≤ 400,000	79 (18.2)	72 (16.7)	68 (15.8)	82 (18.9)
> 400,000	25 (5.7)	24 (5.6)	24 (5.6)	17 (3.9)
CD4 cell count (/µL)				
Mean (SD)	437 (223.7)	426 (212.3)	414 (206.8)	431 (226.8)
CD4 cell count category (/µL), n (%)				
< 50	10 (2.3)	12 (2.8)	14 (3.3)	15 (3.4)
≥ 50 to < 200	48 (11.0)	41 (9.5)	40 (9.3)	49 (11.3)
≥ 200 to < 350	103 (23.7)	111 (25.7)	115 (26.7)	89 (20.5)
≥ 350 to < 500	122 (28.0)	135 (31.3)	134 (31.2)	149 (34.3)
≥ 500	152 (34.9)	133 (30.8)	127 (29.5)	133 (30.6)
HIV risk factors[a], n (%)				
Heterosexual sex	104 (23.9)	103 (23.8)	106 (24.6)	116 (26.7)
Homosexual sex	321 (73.8)	327 (75.7)	331 (76.8)	318 (73.1)
IV drug use	[redacted]	[redacted]	[redacted]	[redacted]
Transfusion	[redacted]	[redacted]	[redacted]	[redacted]
Vertical transmission	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
HIV disease status, n (%)				
Asymptomatic	402 (92.6)	406 (94.2)	378 (88.1)	396 (91.7)
Symptomatic	23 (5.3)	15 (3.5)	30 (7.0)	20 (4.6)
AIDS	9 (2.1)	10 (2.3)	[redacted]	[redacted]
Unknown	1 (0.2)	1 (0.2)	2 (0.5)	3 (0.7)
$eGFR_{CG}$ (mL/min)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]

BMI = body mass index; COBI = cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FTC = emtricitabine; IV = intravenous; SD = standard deviation; RNA = ribonucleic acid; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
Note: Safety analysis set unless otherwise specified.
[a] A patient may fit more than one category of HIV risk factors; therefore, percentages may add to > 100.
Source: Clinical Study Reports, sources 104[2] and 111.[3]

TABLE 11: SUMMARY OF BASELINE CHARACTERISTICS — VIROLOGICALLY SUPPRESSED ADULTS (RANDOMIZED CONTROLLED TRIALS)

Characteristic	Study 109		Study 1089	
	EVG/COBI/FTC/TAF (N = 959)	FTC/TDF + 3rd Drug (N = 477)	FTC/TAF + 3rd Drug (N = 333)	FTC/TDF + 3rd Drug (N = 330)
Age (y)				
Mean (SD)	41 (10.1)	41 (10.1)	47 (9.9)	48 (9.7)
Median	41	40	48	49
Min, max	21, 77	22, 69	22, 78	22, 79
Sex, n (%)				
Male	856 (89.3)	427 (89.5)	285 (85.6)	276 (83.6)
Race, n (%)				
White	651 (67.9)	314 (65.8)	244 (73.3)	253 (76.7)
Black	169 (17.6)	102 (21.4)	69 (20.7)	67 (20.3)
Asian	59 (6.2)	35 (7.3)	[redacted]	[redacted]
Other	80 (8.3)	26 (5.5)	[redacted]	[redacted]
BMI (kg/m^2)				
Mean (SD)	26.6 (5.3)	26.9 (5.3)	27.3 (5.54)	27.6 (5.76)
HIV-1 RNA (log_{10} copies/mL) at baseline				
Mean (SD)	NR	NR	NR	NR
HIV-1 RNA category (copies/mL), n (%)				
<50	943 (98.3)	466 (97.7)	[redacted]	[redacted]
≥50	16 (1.7)	11 (2.3)	[redacted]	[redacted]
CD4 cell count (/µL)				
Mean (SD)	701 (261.8)	689 (248.0)	691 (272.6)	667 (272.3)
CD4 cell count category (/µL), n (%)				
<50	0	0	[redacted]	[redacted]
≥50 to <200	5 (0.5)	4 (0.8)	[redacted]	[redacted]
≥200 to <350	54 (5.6)	25 (5.2)	[redacted]	[redacted]
≥350 to <500	151 (15.7)	70 (14.7)	[redacted]	[redacted]
≥500	749 (78.1)	378 (79.2)	[redacted]	[redacted]
HIV risk factors[a], n (%)				
Heterosexual sex	216 (22.5)	101 (21.2)	75 (22.5)	92 (27.9)
Homosexual sex	753 (78.5)	375 (78.6)	234 (70.3)	220 (66.7)
IV drug use	9 (0.9)	5 (1.0)	[redacted]	[redacted]
Transfusion	2 (0.2)	2 (0.4)	[redacted]	[redacted]
Vertical transmission	0	0	[redacted]	[redacted]
Unknown	17 (1.8)	12 (2.5)	[redacted]	[redacted]
Other	8 (0.8)	7 (1.5)	[redacted]	[redacted]
HIV disease status, n (%)				
Asymptomatic	NR	NR	[redacted]	[redacted]
Symptomatic	NR	NR	[redacted]	[redacted]
AIDS	NR	NR	[redacted]	[redacted]
Unknown	NR	NR	[redacted]	[redacted]

Characteristic	Study 109		Study 1089	
	EVG/COBI/FTC/TAF (N = 959)	FTC/TDF + 3rd Drug (N = 477)	FTC/TAF + 3rd Drug (N = 333)	FTC/TDF + 3rd Drug (N = 330)
$eGFR_{CG}$ (mL/min)				
Mean (SD)	111.9 (33.4)	112.1 (32.7)	[redacted]	[redacted]
Min, max	48, 344.1	53.7, 304.8	[redacted]	[redacted]

BMI = body mass index; COBI = cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FTC = emtricitabine; IV = intravenous; RNA = ribonucleic acid; SD = standard deviation; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
Note: Safety analysis set unless otherwise specified.
[a] A patient may fit more than one category of HIV risk factors; therefore, percentages may add to > 100.
Source: Clinical Study Reports, studies 109[6] and 1089,[16] pp. 69 to 71.

TABLE 12: SUMMARY OF BASELINE CHARACTERISTICS — SPECIAL POPULATIONS (OPEN-LABEL SINGLE-ARM)

Characteristic	Study 112 (Reduced Kidney Function)		Study 106 (Adolescents)
	Switch (N = 242)	ART-Naive (N = 6)	ART-Naive (N = 48)
	EVG/COBI/FTC/TAF		EVG/COBI/FTC/TAF
Age (y)			
Mean (SD)	58 (9.9)	[redacted]	[redacted]
Median	58	[redacted]	15
Min, max	24, 82	[redacted]	12, 17
Sex, n (%)			
Male	192 (79.3)	6 (100)	20 (41.7)
Race, n (%)			
White	152 (62.8)	2 (33.3)	0
Black	44 (18.2)	3 (50.0)	42 (87.5)
Asian	34 (14.0)	1 (16.7)	6 (12.5)
Other	12 (5.0)	0	0
BMI (kg/m^2)			
Mean (SD)	[redacted]	[redacted]	[redacted]
HIV-1 RNA (log_{10} copies/mL) at baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
HIV-1 RNA category (copies/mL), n (%)			
< 50	236 (97.5)	[redacted]	NR
≥ 50 to ≤ 100,000	6 (2.5)	[redacted]	NR
≤ 100,000	NR	NR	38 (79.2)
> 100,000	NR	NR	10 (20.8)
> 100,000 to ≤ 400,000	[redacted]	[redacted]	NR
> 400,000	[redacted]	[redacted]	NR
CD4 cell count (/µL)			
Mean (SD)	[redacted]	[redacted]	[redacted]
CD4 cell count category (/µL), n (%)			
< 50	[redacted]	[redacted]	NR
≤ 199	[redacted]	[redacted]	4 (8.3)
≥ 50 to < 200	[redacted]	[redacted]	NR

Characteristic	Study 112 (Reduced Kidney Function)		Study 106 (Adolescents)
	Switch (N = 242)	ART-Naive (N = 6)	ART-Naive (N = 48)
	EVG/COBI/FTC/TAF		EVG/COBI/FTC/TAF
≥ 200 to ≤ 349	[redacted]	[redacted]	9 (18.8)
≥ 200 to < 350	[redacted]	[redacted]	NR
≥ 350 to ≤ 499	[redacted]	[redacted]	18 (37.5)
≥ 350 to < 500	[redacted]	[redacted]	NR
≥ 500	[redacted]	[redacted]	17 (35.4)
HIV risk factors,[a] n (%)			
Heterosexual sex	[redacted]	[redacted]	[redacted]
Homosexual sex	[redacted]	[redacted]	[redacted]
IV drug use	[redacted]	[redacted]	[redacted]
Transfusion	[redacted]	[redacted]	[redacted]
Vertical transmission	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
HIV disease status, n (%)			
Asymptomatic	180 (74.4)	[redacted]	40 (83.3)
Symptomatic	28 (11.6)	[redacted]	8 (16.7)
AIDS	34 (14.0)	[redacted]	0
Unknown	0	[redacted]	0
eGFR[b]			
Mean (SD)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]

ART = antiretroviral therapy; BMI = body mass index; COBI = cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FTC = emtricitabine; IV = intravenous; RNA = ribonucleic acid; SD = standard deviation; TAF= tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
Note: Safety analysis set unless otherwise specified.
[a] A patient may fit more than one category of HIV risk factors; therefore, percentages may add to > 100.
[b] For study 112, eGFR is by Cockcroft–Gault formula (mL/min); for study 106, eGFR is by original Schwartz formula ($mL/min/1.73m^2$)
Source: Clinical Study Reports, studies 112 [4] and 106.[5]

3.2.3 Interventions

In five of the six included studies, the intervention was a fixed-dose combination tablet of EVG/COBI/FTC/TAF (150 mg/150 mg/200 mg/10 mg).[2-6] In one study, the intervention was FTC/TAF (200 mg/10 mg or 200 mg/25 mg) plus a third drug taken orally once daily.[16] The 200 mg/10 mg dose of FTC/TAF was used when the third drug was an HIV-1 PI boosted by either ritonavir or COBI; otherwise, the 200 mg/25 mg dose of FTC/TAF was used.

In studies 104 and 111, the comparator was a fixed-dose combination tablet of EVG/COBI/FTC/TDF (150 mg/150 mg/200 mg/300 mg) taken orally once daily. Blinding was achieved in both trials through a double-dummy design that used matching placebos for both study treatments. In study 109, patients on an ART regimen consisting of FTC/TDF + a third drug switched in an open-label fashion to EVG/COBI/FTC/TAF or remained on their pre-existing regimen. In study 1089, patients on an ARV regimen consisting of FTC/TDF + a third drug switched in a double-blind manner to FTC/TAF + the pre-existing third drug or remained on their pre-existing regimen. Eligible third drugs in this study were

ATV/r, LPV/r, DRV/r, EFV, RPV, NVP, RAL, DTG, and MVC (0, Table 31). In the single-arm studies 112 and 106, all patients received open-label EVG/COBI/FTC/TAF.

3.2.4 Outcomes

a) Efficacy

Viral Suppression

The primary efficacy outcome for studies 104, 111, 109, and 1089 was the percentage of patients with HIV-1 RNA VL suppression of < 50 copies/mL in the week 48 analysis window (days 294 to 377, inclusive) using the FDA-defined snapshot analysis. In this analysis, patients whose last available HIV-1 RNA value in the week 48 analysis window was < 50 copies/mL were considered to have had a response, whereas patients whose last available 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 not to have had a response. In studies 112 and 106, the primary efficacy outcome was the percentage of patients with HIV-1 RNA VL suppression of < 50 copies/mL in the week 24 analysis window using the FDA-defined snapshot analysis. In study 112, the window was defined from days 140 to 209 (inclusive), whereas in study 106, it was from days 140 to 195 (inclusive). When available, data on virological response at the longest study time point (i.e., 96 weeks for studies 104 and 111 and 48 weeks for study 112) were presented.

Viral Resistance

All studies measured viral resistance at baseline for all patients. Follow-up testing was also done for those patients who failed to achieve virologic success.

Health-Related Quality of Life

Patient health-related quality of life (HRQoL) was evaluated with the EuroQol five-dimensional three-level instrument (EQ-5D-3L) in three studies (104, 111, and 109). [redacted] In [redacted] 109 [redacted], HRQoL was assessed using the Short Form 36 Health Survey (SF-36).

Treatment Adherence

Treatment adherence was reported in all included studies. Treatment adherence for the active drug was measured based on pill counts for all patients. Data were presented using descriptive analyses**.**

Harms

Safety data (AEs, serious adverse events [SAEs], withdrawals due to adverse events [WDAEs], and notable harms) were presented through week 48 for studies 104, 111, 109, 1089, and through week 24 for studies 112 and 106.

3.2.5 Statistical Analysis

For studies 104 and 111, sample sizes were based on an estimated response (HIV-1 RNA < 50 copies/mL at week 48) of 85% for each treatment group, a non-inferiority (NI) margin of 12%, power of at least 95%, and a one-sided significance level of 0.025. Both studies estimated requiring a sample size of 840 patients (420 in each treatment arm). NI was evaluated using a conventional 95% confidence interval (CI) approach against the 12% NI margin, which was previously accepted by the FDA.[40,41] Two interim data analyses were performed at weeks 12 and 24, each of which spent an alpha of 0.00001. Therefore,

the significance level for the two-sided test in the primary analysis at week 48 was set at 0.04998, which corresponded to a 95.002% CI. If non-inferiority of EVG/COBI/FTC/TAF versus EVG/COBI/FTC/TDF was established, the same 95.002% CI was used to evaluate superiority; if the lower bound of the 95.002% CI was greater than 0, superiority of EVG/COBI/FTC/TAF over EVG/COBI/FTC/TDF was established. The full analysis set (FAS) was used for the primary efficacy end point analysis and the superiority evaluation, and a secondary analysis based on the per-protocol (PP) analysis set was conducted to evaluate the robustness of the primary analysis results.

A similar approach was followed to analyze the primary efficacy outcome in studies 109 and 1089, except that, in study 109, only one interim data analysis was performed at week 24, which set the significance level for the two-sided test in the primary analysis at 0.0499, corresponding to a 95.01% CI. In study 1089, sample sizes were based on an estimated response (HIV-1 RNA < 50 copies/mL at week 48) of 87% for each treatment group, an NI margin of 10%, power of at least 95%, and a one-sided significance level of 0.025.

In studies 104 and 111, the changes from baseline in $eGFR_{CG}$ between the treatment groups were compared using a two-sided Wilcoxon rank sum test. Both studies featured four key alpha-protected safety end points, of which two (percentage changes from baseline in bone mineral density [BMD] at the hip or spine at week 48) were of interest. Percentage change from baseline in hip and spine BMD were compared between the treatment groups using an analysis of variance (ANOVA) model, which included treatment as a fixed effect. The analyses of percentage change from baseline in hip and spine BMD were performed using dual-energy X-ray absorptiometry (DXA) analysis set in two ways: DXA analysis set using observed data, and secondly, using imputed data, for which the last post-baseline observation was carried forward.

Study 109 featured a similar approach as above to evaluate changes from baseline in $eGFR_{CG}$ between the treatment groups, except that patients who received EFV/TDF/FTC (an unboosted regimen) were excluded from the analysis. The analysis to evaluate BMD at the hip or spine was similar to the above, except that the ANOVA model included prior treatment regimen and study treatment as fixed effects. In study 1089, the sample size of 330 patients in each group also provided 90% power to detect a 1% difference in percentage change from baseline hip and spine BMD at week 48 between the FTC/TAF and FTC/TDF treatment groups, respectively. In this power assessment, it was assumed that the standard deviation (SD) for percentage BMD decrease was 3.5% (based on Gilead study GS-99-903) and that the two-sided Wilcoxon test was conducted at a 0.025 level.[16]

In studies 111, 104, and 109, multiplicity adjustments were conducted to control for the overall type I error in the assessment of the primary efficacy end point and the four key safety end points. Hypothesis testing was performed in sequential order. If non-inferiority for the primary outcome was established, multiplicity adjustments were performed for the following safety end points using a fallback procedure in the sequential order given below with pre-specified two-sided alpha levels:

a) Hip BMD (alpha = 0.02)
b) Spine BMD (alpha = 0.01)
c) Serum creatinine (alpha = 0.01998)
d) Treatment-emergent proteinuria (alpha = 0.00)

Multiplicity adjustments were also performed in study 1089, with a fallback procedure in the sequential order given below with pre-specified two-sided alpha levels:

a) Hip BMD (alpha = 0.02)
b) Spine BMD (alpha = 0.02998)

In studies 112 and 106, notable kidney and bone system harms were summarized descriptively.

b) Analysis populations

All six studies used the FAS as the primary analysis set for efficacy analyses; the FAS included all patients who were randomized into the study and received at least one dose of the study drug. In the FAS, patients were grouped according to the treatment to which they were randomized. The PP analysis set included all randomized patients who received at least one dose of the study drug and did not have any major protocol violations. In this set, patients were grouped according to the treatment they actually received. The safety analysis set included all randomized patients who received at least one dose of the study drug, but grouped participants according to the treatment they actually received. This was the primary analysis set for most of the safety analyses.

Studies 104, 111, 109, and 1089 included a hip DXA analysis set and a spine DXA analysis set, both of which included all patients who were randomized, received at least one dose of the study drug, and had non-missing baseline BMD values; patients were grouped according to the treatment they actually received. Study 106 included a total body less head (TBLH) DXA analysis set rather than a hip DXA analysis set.

3.3 Patient Disposition

3.3.1 Study 104

In study 104, a total of 872 patients were randomized, with [redacted] patients ([redacted] in the EVG/COBI/FTC/TAF group and [redacted] in the EVG/COBI/FTC/TDF group) never receiving treatment. A total of 21 (4.8%) and 27 (6.3%) patients discontinued from the EVG/COBI/FTC/TAF and EVG/COBI/FTC/TDF groups, respectively. Reasons for premature discontinuation across the groups varied, with loss to follow-up ([redacted]% versus [redacted]%), consent withdrawal ([redacted]% versus [redacted]%), and AEs ([redacted]% versus [redacted]%) being the most common in the EVG/COBI/FTC/TAF and EVG/COBI/FTC/TDF groups, respectively (Table 13).

3.3.2 Study 111

In study 111, a total of 872 patients were randomized, with [redacted] patients ([redacted] in the EVG/COBI/FTC/TAF group and [redacted] in the EVG/COBI/FTC/TDF group) never receiving treatment. A total of 18 (4.2%) and 28 (6.4%) patients discontinued from the EVG/COBI/FTC/TAF and EVG/COBI/FTC/TDF groups, respectively. Reasons for premature discontinuation across the groups varied, with loss to follow-up ([redacted]% versus [redacted]%), consent withdrawal ([redacted]% versus [redacted]%), and investigator's discretion ([redacted] versus [redacted]%) being the most common in the EVG/COBI/FTC/TAF and EVG/COBI/FTC/TDF groups, respectively (Table 13).

3.3.3 Study 109

In study 109, a total of 1,443 patients were randomized, with seven patients (four in the EVG/COBI/FTC/TAF arm and three in the FTC/TDF + a third drug arm) never receiving treatment. A total of 32 (3.3%) and 40 (8.3%) patients discontinued from the EVG/COBI/FTC/TAF and FTC/TDF + a third drug arms, respectively. Reasons for premature discontinuation across the arms varied, with consent withdrawal (0.8% versus 3.4%), AE (0.9% versus 12.5%), and loss to follow-up (0.6%versus 1.4%) being the most common in the EVG/COBI/FTC/TAF and FTC/TDF + a third drug groups, respectively (Table 14).

3.3.4 Study 1089

In study 1089, a total of 668 patients were randomized, with five patients (one in the FTC/TAF + a third drug arm and three in the FTC/TDF + a third drug arm) never receiving treatment. A total of 19 (5.7%) and 14 (4.2%) patients discontinued from the FTC/TAF + a third drug and FTC/TDF + a third drug arms, respectively. Reasons for premature discontinuation across the arms varied in some cases, with withdrawal of consent (3% in both arms), AE (1.2% versus 0%), and loss to follow-up (0.6% versus 0.3%) being the most common in the FTC/TAF + a third drug and FTC/TDF + a third drug arms, respectively (Table 14).

TABLE 13: PATIENT DISPOSITION — TREATMENT-NAIVE ADULTS (RANDOMIZED CONTROLLED TRIALS)

Week 48	Study 104		Study 111	
	EVG/COBI /FTC/TAF	EVG/COBI /FTC/TDF	EVG/COBI /FTC/TAF	EVG/COBI /FTC/TDF
Screened, n	1105		1070	
Randomized, n	438	434	435	437
Randomized and never treated, n	3	2	4	2
Discontinued, n (%)	21 (4.8)	27 (6.3)	18 (4.2)	28 (6.4)
Adverse event	3 (0.7)	4 (0.9)	4 (0.9)	7(1.6)
Death	0	1 (0.2)	1 (0.2)	2 (0.5)
Pregnancy	0	0	0	0
Lack of efficacy	0	1 (0.2)	0	1 (0.2)
Investigator's discretion	0	0	0	6 (1.4)
Non-compliance with study drug	1 (0.2)	1 (0.2)	1 (0.2)	0
Protocol violation	3 (0.7)	3 (0.7)	0	1 (0.2)
Withdrew consent	9 (2.1)	7 (1.6)	4 (0.9)	9 (2.1)
Lost to follow-up	5 (1.1)	10 (2.3)	10 (2.3)	9 (2.1)
Safety analysis set, n (%)	435 (99.3)	432 (99.5)	431 (99.1)	435 (99.5)
Full analysis set, n (%)	435 (99.3)	432 (99.5)	431 (99.1)	435 (99.5)
Week 48 PP analysis set, n (%)	404 (92.2)	397 (91.5)	397 (91.3)	392 (89.7)
Hip DXA analysis set, n (%)	424 (96.8)	424 (97.7)	412 (94.7)	424 (97.0)
Spine DXA analysis set, n (%)	427 (97.5)	425 (97.9)	418 (96.1)	425 (97.3)

COBI = cobicistat; DXA = dual-energy X-ray absorptiometry; EVG = elvitegravir; FTC = emtricitabine; PP = per-protocol; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.
Note: The denominator for percentages was based on the number of patients randomized.
Source: Clinical Study Reports, studies 104[2] and 111.[3]

TABLE 14: PATIENT DISPOSITION — VIROLOGICALLY SUPPRESSED ADULTS (RANDOMIZED CONTROLLED TRIALS)

Week 48	Study 109		Study 1089	
	EVG/COBI /FTC/TAF	FTC/TDF +3rd Drug	FTC/TAF +3rd Drug	FTC/TDF +3rd Drug
Screened, n	1,559		780	
Randomized, n	963	480	334	334
Randomized and never treated, n	4	3	1	4
Discontinued, n (%)	32 (3.3)	40 (8.3)	19 (5.7)	14 (4.2)
Adverse event	9 (0.9)	12 (2.5)	7 (2.1)	3(0.9)
Death	4 (0.4)	0	[redacted]	[redacted]
Pregnancy	0	0	[redacted]	[redacted]
Lack of efficacy	1 (0.1)	0	[redacted]	[redacted]
Investigator's discretion	2 (0.2)	3 (0.6)	1 (0.3)	0
Non-compliance with study drug	2 (0.2)	2 (0.4)	[redacted]	[redacted]
Protocol violation	0	0	0	2 (0.6)
Withdrew consent	8 (0.8)	16 (3.4)	10 (3.0)	10 (3.0)
Lost to follow-up	6 (0.6)	7 (1.4)	[redacted]	[redacted]
Safety analysis set, n (%)	959 (99.6)	477 (99.4)	333 (99.7)	330 (98.8)
Full analysis set, n (%)	959 (99.6)	477 (99.4)	333 (99.7)	330 (98.8)
Week 48 PP analysis set, n (%)	921 (95.6)	440 (91.7)	[redacted]	[redacted]
Hip DXA analysis set, n (%)	NR	NR	321 (96.1)	317 (94.9)
Spine DXA analysis set, n (%)	NR	NR	321 (96.1)	320 (95.8)

COBI = cobicistat; DXA = dual-energy X-ray absorptiometry; EVG = elvitegravir; FTC = emtricitabine; PP = per-protocol; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.
Note: The denominator for percentages was based on the number of patients randomized.
Source: Study 109, Mills et al. (2016);[37] study 1089 Clinical Study Report[16] pp. 67, 410, 411.

3.3.5 Study 112

In study 112, a total of 252 patients were enrolled, with four patients (all in the switch group) never receiving treatment. Among patients in the switch group, 10 (4.1%) discontinued, four (1.7%) due to an AE, one (0.4%) due to protocol violation, two (0.8%) due to loss to follow-up, and three (1.2%) due to consent withdrawal. None of the six treatment-naive patients discontinued (Table 15).

3.3.6 Study 106

In study 106, a total of 48 patients were enrolled, of whom none prematurely discontinued from the study (Table 15).

TABLE 15: PATIENT DISPOSITION — SPECIAL POPULATIONS (OPEN-LABEL SINGLE-ARM STUDIES)

Week 24	Study 112 (Reduced Kidney Function)				Study 106 (Adolescents)
	Switch			ART-Naive	ART-Naive
	BL $eGFR_{CG}$ < 50 mL/min	BL $eGFR_{CG}$ ≥ 50 mL/min	Total		
	EVG/COBI/FTC/TAF				EVG/COBI/FTC/TAF
Screened, n	[redacted]	[redacted]	[redacted]	[redacted]	63
Enrolled, n	[redacted]	[redacted]	[redacted]	[redacted]	48
Enrolled and never treated, n	[redacted]	[redacted]	[redacted]	[redacted]	0
Discontinued, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	0
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	0
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]	0
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	0
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	0
Safety analysis set, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	48 (100)
Full analysis set, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	23 (47.9)
Hip DXA analysis set, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NA
Spine DXA analysis set, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TBLH DXA analysis set, n (%)	[redacted]				[redacted]

ART = antiretroviral therapy; BL = baseline; COBI = cobicistat; DXA = Dual-energy X-ray Absorptiometry; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FTC = emtricitabine; NA = not applicable; PP = per-protocol; TAF = tenofovir alafenamide; TBLH = total body less head; TDF = tenofovir disoproxil fumarate.
Note: The denominator for percentages was based on the number of patients enrolled.
Source: Study 112 Clinical Study Report (CSR),[4] study 106 CSR.[5]

3.4 Exposure to Study Treatments

Duration of exposure to study drugs was the number of weeks between the first and last dose of the study drug. If the last dose date was completely missing, if only the year was known, or if a patient was still on the study drug, the latest of the study drug's start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the date of the last dose. Exposure time to the study drug (in weeks) was similar between treatment groups within each study, but varied from study to study (Table 28, Table 29, and Table 30).

3.5 Critical Appraisal

3.5.1 Internal Validity

Studies 104 and 111 were double-blind, double-dummy, randomized, active-controlled, parallel-group trials with appropriate randomization and allocation concealment procedures. Baseline characteristics were similar across treatment groups in both trials. Both studies surpassed the required sample size of 840 patients (420 in each treatment arm). Even though both trials were designed to test the non-inferiority of the FTC/TAF-based regimen (EVG/COBI/FTC/TAF) versus the FTC/TDF-based regimen (EVG/COBI/FTC/TDF), the primary efficacy outcome was tested using the FAS, which was inherently a modified intention-to-treat (ITT) analysis that could potentially bias the results in favour of a finding of non-inferiority. Nevertheless, secondary analyses using the PP analysis set were conducted to corroborate the primary findings, hence confirming the results.

Further, both studies appropriately tested for superiority of EVG/COBI/FTC/TAF after non-inferiority was established. In addition, the significance level for the two-sided test in the primary analysis appropriately accounted for two interim data analyses. The number of premature discontinuations in both trials was low. In both studies, a two-sided Wilcoxon rank sum test was used to evaluate changes from baseline in $eGFR_{CG}$ between the treatment groups. While the use of a non-parametric statistical hypothesis test (Wilcoxon rank sum test) was appropriate given the presentation of medians and interquartile ranges, an explicit rationale for why a parametric test (evaluating means and SDs) was not used would have increased the transparency of the analyses.

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 and spine BMD between the treatment groups. The analyses of percentage change from baseline in hip and spine BMD were performed using observed and imputed data, for which the last post-baseline observation was carried forward. The number of patients for whom data were imputed was unclear, but appeared to range from four to 11 patients (0.5% to 1.3%) across the treatment arms in the two studies. Carrying the last observation forward may inappropriately ignore deterioration and artificial stabilization of bone loss among patients who dropped out. On the other hand, observed data could also be biased if the probability of withdrawal is correlated with the risk or extent of bone loss.

Studies 109 and 1089 were designed similarly to the above studies, except that patients in study 109 were not blinded to treatment assignments during the trial. However, lack of blinding is not a concern for the primary efficacy outcome (virologic success), which was not a subjective measure, although it should be considered when interpreting the HRQoL data. Apart from this difference, studies 109 and 1089 feature similar strengths and limitations as the above studies. Further, the ANOVA in studies 109 and 1089 included current and prior treatment regimen as fixed effects.

Studies 112 and 106 were open-label, single-arm studies. Due to the non-randomized nature of open-label studies, the internal validity of these studies is unknown.

3.5.2 External Validity

The choice of primary efficacy outcome and NI margin (12% for all RCTs, except for study 1089, which used a NI margin of 10%) were consistent with FDA guidance for efficacy evaluations of HIV therapies; likewise, the presentation of 48-week data for all studies was consistent with the standards described in the FDA guidance for this therapeutic category; however, the 48-week time point was secondary to the 24-week time point in studies 112 and 106. HRQoL was reported only in the four RCTs, and not in the two cohort studies. Both the input from patient groups and the consulting clinical expert, however, did not expect a change in quality of life (QoL) with FTC/TAF-based therapies versus existing therapies (i.e., between treatment groups).

In studies 104 and 111, FTC/TAF-based regimens (EVG/COBI/FTC/TAF) were compared against FTC/TDF-based regimens (EVG/COBI/FTC/TDF), both of which are DHHS-preferred initial regimens. In study 109, patients were randomized to be switched to an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from one of four FTC/TDF-based regimens (EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/COBI + FTC/TDF, and ATV/r + FTC/TDF), or to remain on their existing regimen. In study 1089, FTC/TAF-based regimens (FTC/TAF + a third drug) were directly compared with other DHHS-recommended FTC/TDF-based regimens.

Most of the trial patients were recruited from US centres. Study 104 included eight Canadian sites. There were five Canadian sites in study 111, 10 in study 109, and four in study 1089. No patients were enrolled from Canadian centres in studies 112 and 106. Additionally, patients with hepatitis B or hepatitis C were excluded from the studies, which leaves the relative efficacy and safety in these patients uncertain.

Given the small number of treatment-naive patients enrolled in study 112, the results are insufficient to draw robust conclusions about the efficacy and safety of FTC/TAF-based regimens (FTC/TAF + a third drug) in treatment-naive patients with reduced kidney function. Furthermore, it is uncertain why a baseline $eGFR_{CG}$ of > 50 mL/min and < 50mL/min was selected as the subgroup criteria in this study; the clinical expert involved in the review indicated that 60 mL/min is typically used as a threshold for kidney functioning.

Study 106 mostly enrolled female patients which, according to the clinical expert consulted by CDR, was most likely due to the fact that most of the population was from HIV-endemic countries or had been infected through vertical transmission. However, the expert did highlight that the most common (66.7% in study 106) risk factor for HIV infection among adolescents is vertical transmission. The expert also indicated that children infected with HIV through vertical transmission are likely to be treated before reaching adolescence; therefore, most adolescents with HIV infection encountered in clinical practice in Canada are likely to be ART-experienced. The small number of adolescent patients in this study also limits our ability to draw conclusions about safety and efficacy in this population.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in section 2.2, Table 6. See Appendix 4 for long-term efficacy outcome data.

3.6.1 Virologic Success (Snapshot Analysis)

In studies 104 and 111, results from the primary (FAS) analyses demonstrated that a similar percentage of patients in the EVG/COBI/FTC/TAF group compared with the EVG/COBI/FTC/TDF group achieved a VL of < 50 copies/mL at week 48 (study 104 difference: 1.0% [95.002% CI, –2.6 to 4.5]; study 111 difference: 3.1% [95.002% CI, –1.0 to 7.1]) (Table 16). Results from the secondary (PP) analysis were consistent with the primary analyses. Further, there were no statistically significant differences in the rates of virologic success by VL subgroups in these studies. In study 1089, the results from the primary (FAS) analyses demonstrated a similar virologic success rate between the two treatment groups (i.e., patients who switched to an FTC/TAF-based regimen (FTC/TAF plus a third drug) (94.3%) versus those who stayed on their pre-existing FTC/TDF-based ART regimen (FTC/TDF plus a third drug) (93.0%)) at week 48, no PP analyses data were provided. In study 109, results from the primary (FAS) analyses demonstrated that statistically significantly more patients who switched to a FTC/TAF-based regimen (EVG/COBI/FTC/TAF) (97.2%) versus those who stayed on their pre-existing FTC/TDF-based regimen (FTC/TDF plus a third drug) (93.1%) achieved VL < 50 copies/mL at week 48 (difference: 4.1% (95% CI, 1.6 to 6.7). However, whether the PP analyses corroborated these findings was uncertain, as no associated measures of precision were reported (Table 17). The efficacy profile of the FTC/TAF-based regimen (EVG/COBI/FTC/TAF) versus the FTC/TDF-based regimen (EVG/COBI/FTC/TDF) at 96 weeks (pooled data from studies 104 and 111) was similar to the 48-week results (see Table 32 in 0).

In study 112, the primary analysis (FAS) demonstrated that the virologic success rates at 24 weeks (snapshot algorithm) were 95.0% and 83.3% among adults who switched to a FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from their existing ARV regimen and among treatment-naive adults who received a

FTC/TAF-based regimen (EVG/COBI/FTC/TAF), respectively (Table 18). The efficacy profile of EVG/COBI/FTC/TAF at 48 weeks was similar to the 24-week results (see 0, Table 33). In study 106, the virologic success rate at 24 weeks (FAS, snapshot algorithm) was 91.3% for 23 ART-naive adolescents receiving EVG/COBI/FTC/TAF.

The virologic success rate data at 96 weeks for studies 109 and 1089 or at 48 weeks for study 106 were not available at the time of this submission.

TABLE 16: KEY EFFICACY OUTCOMES — TREATMENT-NAIVE ADULTS (RANDOMIZED CONTROLLED TRIALS, WEEK 48)

Virologic Success (Snapshot Analysis, FAS at Week 48[a])		Study 104		Study 111	
		EVG/COBI/FTC/ TAF	EVG/COBI/FTC/ TDF	EVG/COBI/FTC/ TAF	EVG/COBI/FTC/ TDF
Overall population					
N	FAS	435	432	431	435
	PP	[redacted]	[redacted]	[redacted]	[redacted]
HIV-1 RNA < 50 copies/mL, N (%)	FAS	405 (93.1)	399 (92.4)	395 (91.6)	385 (88.5)
	PP	[redacted]	[redacted]	[redacted]	[redacted]
Difference in % (95% CI);[b] *P* value	FAS	1.0 (–2.6 to 4.5); *P* = 0.58[c]		3.1 (–1.0 to 7.1); *P* = 0.13[c]	
	PP	[redacted]		[redacted]	
By VL subgroup					
≤ 100,000 copies/mL		[redacted]	[redacted]	[redacted]	[redacted]
Difference in % (95% CI); *P* value		[redacted]		[redacted]	
> 100,000 copies/mL		[redacted]	[redacted]	[redacted]	[redacted]
Difference in % (95% CI); *P* value		[redacted]		[redacted]	

CI = confidence interval; COBI = cobicistat; EVG = elvitegravir; FAS = full analysis set; FTC = emtricitabine; PP = per-protocol; RNA = ribonucleic acid; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; VL = viral load.
[a] FAS unless otherwise specified.
[b] The CI for studies 104 and 111 is 95.002%.
[c] Superiority test was conducted if non-inferiority was achieved.
Source: Study 104 Clinical Study Report (CSR),[2] study 111 CSR. [3]

TABLE 17: KEY EFFICACY OUTCOMES — VIROLOGICALLY SUPPRESSED ADULTS (RANDOMIZED CONTROLLED TRIALS, WEEK 48)

Virologic Success (Snapshot Analysis, FAS at Week 48)[a]		Study 109		Study 1089	
		EVG/COBI/FTC/TAF	FTC/TDF + 3rd Drug	FTC/TAF + 3rd Drug	FTC/TDF + 3rd Drug
N	FAS	959	477	333	330
	PP	921	440	304	305
HIV-1 RNA < 50 copies/mL, N (%)	FAS	932 (97.2)	444 (93.1)	314 (94.3)	307 (93.0)
	PP	913 (99.1)	435 (98.9)	[redacted]	[redacted]
Difference in % (95% CI);[b] *P* value	FAS	4.1 (1.6 to 6.7); *P* = 0.0002[c]		1.3 (−2.5 to 5.1); *P* = 0.5[c]	
	PP	0.3 (NR); *P* = NR		[redacted]	[redacted]

CI = confidence interval; COBI = cobicistat; EVG = elvitegravir; FAS = full analysis set; FTC = emtricitabine; NR = not reported; PP = per-protocol; RNA = ribonucleic acid; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.
Note: no subgroup analysis based on baseline RNA copies (≤ 100,000 copies/mL versus > 100,000 copies/mL) was done in studies 109 and 1089.
[a] FAS unless otherwise specified.
[b] The CI for study 109 is 95.01%. For study 1089, it is 95.002%.
[c] The *P* value for the superiority test comparing the percentages of virologic success was from the Cochran–Mantel–Haenszel test stratified by a third drug (ritonavir-boosted protease inhibitors versus others).
Source: Mills et al. (2016),[37] study 1089 Clinical Study Report, p. 76.[16]

TABLE 18: KEY EFFICACY OUTCOMES — SPECIAL POPULATIONS (OPEN-LABEL SINGLE-ARM, WEEK 24)

Virologic Success (Snapshot Analysis, FAS at Week 24)	Study 112 (Reduced Kidney Function)				Study 106 (Adolescents)
	Switch to EVG/COBI/FTC/TAF			ART-Naive	ART-Naive
	BL $eGFR_{CG}$ < 50 mL/min	BL $eGFR_{CG}$ ≥ 50 mL/min	Total		
	EVG/COBI/FTC/TAF				EVG/COBI /FTC/TAF
WEEK 24					
N	80	162	242	6	23
HIV-1 RNA < 50 copies/mL, N (%)	76 (95.0)	154 (95.1)	230 (95.0)	5 (83.3)	21 (91.3)

ART = antiretroviral therapy; BL = baseline; COBI= cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FAS = full analysis set; FTC = emtricitabine; RNA = ribonucleic acid; TAF= tenofovir alafenamide fumarate.
Source: Study 112 Clinical Study Report (CSR),[4] study 106 CSR.[5]

3.6.2 Other Efficacy Outcomes

a) Resistance development

Across studies 104 and 111, a total of seven (0.8%) and five (0.6%) patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) and an FTC/TDF-based regimen (EVG/COBI/FTC/TDF), respectively, who experienced virologic failure, developed primary genotypic resistance through week 48 (see Appendix 5, Table 34). In study 109, one patient who switched to the EVG/COBI/FTC/TAF group developed resistance to FTC (M184M/I) through week 48. In study 1089, one (0.3%) patient receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) and no patients receiving an FTC/TDF-based regimen (EVG/COBI/FTC/TDF) developed genotypic resistance through week 48 (see Table 35, Appendix 5). In studies 112 and 106,

through week 48, no patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) developed new resistance or mutations that were not already present at baseline (see Appendix 5).

b) Health-related quality of life

Across studies 104, 111, 109 [redacted] There were [redacted] in change from baseline in the EuroQol index score and the associated visual analogue scale from baseline through week 48 between patients receiving FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) and FTC/TDF-based regimens (EVG/COBI/FTC/TDF or FTC/TDF + a third drug). In [redacted] 109 [redacted], there were [redacted] differences in change from baseline in each sub-component of the SF-36 physical and mental function domains through week 48 between patients who switched to [redacted] EVG/COBI/FTC/TAF [redacted] from a pre-existing [redacted] regimen [redacted] FTC/TDF + a third ARV drug [redacted] and those who remained on their existing regimen.

c) Adherence

Adherence to the study drug regimen was calculated based on pill counts for the active drug only. Across all studies, at least 77% of patients in each treatment arm achieved adherence rates of ≥ 95% at week 48 (see Table 19, Table 20, and Table 21).

TABLE 19: ADHERENCE TO THE STUDY DRUG – TREATMENT-NAIVE ADULTS (RANDOMIZED CONTROLLED TRIALS, SAFETY ANALYSIS SET)

Adherence to Study Drug[a,b]	Study 104		Study 111	
	EVG/COBI /FTC/TAF (N = 435)	EVG/COBI /FTC/TDF (N = 432)	EVG/COBI /FTC/TAF (N = 431)	EVG/COBI /FTC/TDF (N = 435)
Number of patients who returned ≥ 1 bottle and have calculable adherence,[a,b] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Study drug adherence rate up to week 48				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Study drug adherence rate up to week 48				
< 80%	[redacted]	[redacted]	[redacted]	[redacted]
≥ 80% to < 90%	[redacted]	[redacted]	[redacted]	[redacted]
≥ 90% to < 95%	[redacted]	[redacted]	[redacted]	[redacted]
≥ 95%	[redacted]	[redacted]	[redacted]	[redacted]

COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; SD = standard deviation; TAF= tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

[a] Adherence was calculated based on pill count for the active drugs only.

[b] The denominator for the percentage of drug adherence category was the number of patients who returned at least one bottle and had calculable drug adherence.

Source: Study 104 Clinical Study Report (CSR)[2] and study 111 CSR.[3]

TABLE 20: ADHERENCE TO THE STUDY DRUG — VIROLOGICALLY SUPPRESSED ADULTS (RANDOMIZED CONTROLLED TRIALS, SAFETY ANALYSIS SET)

	Study 109		Study 1089	
	EVG/COBI /FTC/TAF (N = 959)	FTC/TDF +3rd Drug (N = 477)	FTC/TAF +3rd Drug (N = 333)	FTC/TDF +3rd Drug (N = 330)
Number of patients who returned ≥ 1 bottle and have calculable adherence,[a,b] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Study drug adherence rate up to week 48				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Study drug adherence rate up to week 48				
< 80%	[redacted]	[redacted]	[redacted]	[redacted]
≥ 80% to < 90%	[redacted]	[redacted]	[redacted]	[redacted]
≥ 90% to < 95%	[redacted]	[redacted]	[redacted]	[redacted]
≥ 95%	[redacted]	[redacted]	[redacted]	[redacted]

COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; SD = standard deviation; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

[a] Adherence was calculated based on pill count for each active drug only.

[b] The denominator for the percentage of drug adherence category was the number of patients who returned at least one bottle and had calculable drug adherence.

Source: Study 109 Clinical Study Report (CSR),[6] and study 1089 CSR.[16]

TABLE 21: ADHERENCE TO THE STUDY DRUG — SPECIAL POPULATIONS (OPEN-LABEL SINGLE-ARM, SAFETY ANALYSIS SET)

	Study 112				Study 106
	Cohort 1: Switch			Cohort 2: ART-NAIVE (N = 6)	ART-Naive (N = 48)
	BL $eGFR_{CG}$ < 50 mL/min (N = 80)	BL $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)		
	EVG/COBI/FTC/TAF				EVG/COBI /FTC/TAF
Number of patients who returned ≥ 1 bottle and have calculable adherence[a],[b] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study drug adherence rate during the study					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study drug adherence rate during the study					
< 80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 80 to < 90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 90 to < 95%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 95%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ART = antiretroviral therapy; BL = baseline; COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; SD = standard deviation; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
[a] Adherence was calculated based on pill count.
[b] The denominator for the percentage of drug adherence category was the number of patients who returned at least one bottle and had
calculable drug adherence.
Source: Study 112 Clinical Study Report(CSR)[4] and study 106 CSR.[5]

3.7 Harms

Only those harms identified in the review protocol are reported below (see Table 6 in section 2.2.1, Protocol).

3.7.1 Adverse Events

Across all six studies, at least 80% of patients in each trial experienced at least one treatment-emergent adverse event (TEAE). The proportion of patients with TEAEs appeared similar between patients randomized to an FTC/TAF-based regimen (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) or a comparator (study 104: [redacted]% versus [redacted]%; study 111: [redacted]% versus [redacted]%; study 109: 86.3% versus 83.7%; study 1089: [redacted]% versus [redacted]; see Table 22). The most common AE (> 10%) in studies 111 and 104 was diarrhea, which occurred more frequently in patients receiving an FTC/TDF-based regimen (EVG/COBI/FTC/TDF). The most common AE in studies 109 and 1089 was upper respiratory tract infections (URTIs); other common AEs (> 10%) were nausea and headache (see Table 23).

In study 112, at least one AE was reported in 209 (86.4%) patients who switched to EVG/COBI/FTC/TAF from their existing ARV regimen (Table 24). The most common AEs reported by these patients were diarrhea (8.7%), arthralgia (8.3%), osteopenia (7.9%), and bronchitis (7.9%). In this study, [redacted] of [redacted] ([redacted]%) patients among the treatment-naive cohort experienced an AE. In study 106, 39 (81.3%) ART-

naive adolescents receiving EVG/COBI/FTC/TAF reported an AE, the most common of which was nausea (22.9%), followed by URTI (20.8%), diarrhea (16.7%), headache (14.6%), and abdominal pain (14.6%).

3.7.2 Serious Adverse Events

In studies 104 and 111, the percentage of patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) who experienced an SAE was slightly higher than among those receiving an FTC/TDF-based regimen (EVG/COBI/FTC/TDF) (study 104: [redacted]% versus [redacted]%; study 111: [redacted]% versus [redacted]%; Table 22). In study 109, 6.8% of patients who switched to an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from a pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug) reported an SAE compared with 7.3% of those who remained on the pre-existing FTC/TDF-based regimen. In study 1089, 5.4% of patients who switched to a FTC/TAF-based regimen (FTC/TAF + a third drug) from a pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug) reported an SAE compared with 4.2% of those who remained on the pre-existing FTC/TDF-based regimen (Table 23).

In study 112, [redacted] ([redacted]%) patients who switched to EVG/COBI/FTC/TAF from their existing ARV regimen reported an SAE; [redacted] of the [redacted] treatment-naive patients experienced an SAE. In study 106, four (8.3%) patients reported an SAE (Table 24).

SAEs were rare, and varied in nature in all studies (including vomiting, appendicitis, and psychotic disorder), with no individual event appearing to occur more frequently in one treatment arm versus another.

3.7.3 Withdrawals Due to Adverse Events

In studies 104, 111, and 109, fewer patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) withdrew due to AEs than those receiving a FTC/TDF-based regimen (EVG/COBI/FTC/TDF or FTC/TDF + a third drug) (study 104: 0.7 % versus 0.9%; study 111: 0.9% versus 1.6%; study 109: 0.9% versus 2.5%). In study 1089, seven (2.1 %) patients receiving an FTC/TAF-based regimen (FTC/TAF + a third drug) withdrew due to AEs, while three (0.9%) patients who remained on the pre-existing FTC/TDF-based regimen (FTC/TDF + third drug) withdrew due to an AE [38] (Table 22 and Table 23).

In study 112, eight (3.3%) of patients who switched to EVG/COBI/FTC/TAF from their existing ART regimen withdrew due to AEs; none of the six treatment-naive patients withdrew due to AEs. In study 106, no ART-naive adolescents receiving EVG/COBI/FTC/TAF withdrew due to AEs (Table 24).

WDAEs were rare and varied in nature in all studies, with no individual event appearing to occur more frequently in one treatment arm versus another.

3.7.4 Mortality

In study 104, one patient in each group died, whereas in study 111, one patient receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) and two patients receiving a FTC/TDF-based regimen (EVG/COBI/FTC/TDF) died. In study 109, four patients who switched to an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from a pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug) died, whereas no patient died in the comparator group. In study 1089, one patient in the FTC/TAF + a third drug group died during the study. In studies 112 and 106, no patients died. Across all studies, no deaths that occurred were considered to be study drug–related or HIV-related (Table 22, Table 23, and Table 24).

3.7.5 Notable Harms

a) Kidney Function

In studies 104 and 111, there were statistically significantly greater decreases in median $eGFR_{CG}$ from baseline to week 48 in patients receiving an FTC/TDF-based regimen (EVG/COBI/FTC/TDF) compared with patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF). The median treatment group difference in study 104 was 3.6 mL/min ($P < 0.001$) and 6.2 mL/min ($P < 0.001$) in study 111 (Table 25). However, in study 104, patients in the FTC/TDF-based regimen group (EVG/COBI/FTC/TDF) had a statistically significantly lower $eGFR_{CG}$ at baseline (119 mL/min versus 113 mL/min; $P = 0.031$). In study 109, at week 48, median $eGFR_{CG}$ increased from baseline among patients who switched to an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from a pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug) (except for patients who switched from EFV/FTC/TDF), but decreased among those patients who stayed on their pre-existing regimens. The difference between groups was statistically significant (median difference: 5.5 mL/min; $P < 0.001$). In study 1089, median changes in $eGFR_{CG}$ values from baseline to week 48 were 8.4 mL/min and 2.8 mL/min for patients receiving FTC/TAF plus a third drug and patients receiving FTC/TDF plus a third drug, respectively (median difference: 5.6 mL/min; $P < 0.001$) (Table 26).

In study 112, the overall median (Q1, Q3) change from baseline in $eGFR_{CG}$ at week 24 was –0.4 (–4.7, 4.5) mL/min for $eGFR_{CG}$ among patients who switched to EVG/COBI/FTC/TAF from their existing ART regimen (Table 27). The subgroup with baseline $eGFR_{CG} < 50$ mL/min had a median increase from baseline in $eGFR_{CG}$ at weeks 24, while the $eGFR_{CG} \geq 50$ mL/min subgroup had a median decrease from baseline to week 24. Among the six treatment-naive patients, the overall median (Q1, Q3) change from baseline in $eGFR_{CG}$ at week 24 was –0.3 (–3.6, 1.3) mL/min. In study 106, the overall median (Q1, Q3) change from baseline in eGFR (according to the Schwartz formula) at week 24 was –20.0 (–32.0, -12.0) mL/min among treatment-naive adolescents receiving EVG/COBI/FTC/TAF.

b) Bone System

In studies 104 and 111, there was a statistically significantly smaller percentage decrease in mean BMD at the hip and spine from baseline to week 48 among patients who received an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) compared with those who received an FTC/TDF-based regimen (EVG/COBI/FTC/TDF) ($P < 0.001$) (Table 25). Analyses of the observed data corroborated the findings of the imputed data.

In study 109, the overall mean BMD at the hip and spine increased in the patients who switched to an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from a pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug) (except those who switched from EFV/TDF/FTC), but decreased among those who stayed on their pre-existing regimens. The difference in least squares mean (95% CI) percentage change in hip BMD at week 48 was 1.81 (1.49 to 2.13); the difference in LSM (95% CI) percentage change in spine BMD at week 48 was 2.00 (1.55 to 2.45). The differences between treatment arms were statistically significant (both $P < 0.0001$).

It was unclear whether these results reflected analyses of the observed or imputed data (Table 26). In study 1089, the overall mean hip BMD decreased in both treatment groups, but there was a statistically significantly greater percentage decrease in patients who switched to an FTC/TAF-based regimen (FTC/TAF + a third drug) from a pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug) compared with those patients who remained on their pre-existing regimen (difference in LSM [95% CI] percentage change in hip BMD at week 48: 1.29 [0.86 to 1.71], $P < 0.001$). The overall mean spine BMD increased in those patients who switched to an FTC/TAF-based regimen (FTC/TAF + a third drug) from a pre-existing

FTC/TDF-based regimen (FTC/TDF + a third drug), but decreased among those who stayed on their pre-existing regimen (difference in LSM [95% CI] percentage change in spine BMD at week 48: 1.74 [1.22 to 2.25], $P < 0.001$). It was unclear whether these results reflected analyses of the observed or imputed data (Table 26).

In study 112, there was an overall numerical increase in mean BMD at the hip and spine in the patients who switched to EVG/COBI/FTC/TAF from their existing ART regimen, and a decrease among the six treatment-naive patients at week 24 (Table 27). In study 106, the overall mean spine and TBLH BMD increased among treatment-naive adolescents (see Table 27).

TABLE 22: HARMS — TREATMENT-NAIVE ADULTS (RANDOMIZED CONTROLLED TRIALS, FREQUENCY > 5%)

	Study 104		Study 111	
	EVG/COBI /FTC/TAF (N = 435)	EVG/COBI /FTC/TDF (N = 432)	EVG/COBI /FTC/TAF (N = 431)	EVG/COBI /FTC/TDF (N = 435)
AEs				
Patients with > 0 AEs, n (%)	396 (91.0)	392 (90.7)	382 (88.6)	390 (89.7)
Most common AEs (> 5%), n (%)				
Diarrhea	78 (17.9)	81 (18.8)	69 (16.0)	83 (19.1)
Nausea	62 (14.3)	75 (17.4)	70 (16.2)	76 (17.5)
Vomiting	23 (5.3)	20 (4.6)	39 (9.0)	34 (7.8)
Fatigue	33 (7.6)	37 (8.6)	38 (8.8)	34 (7.8)
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
URTI	50 (11.5)	64 (14.8)	49 (11.4)	45 (10.3)
Nasopharyngitis	35 (8.0)	31 (7.2)	43 (10.0)	49 (11.3)
Syphilis	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	NR	NR
Back pain	27 (6.2)	25 (5.8)	33 (7.7)	32 (7.4)
Arthralgia	26 (6.0)	17 (3.9)	35 (8.1)	22 (5.1)
Osteopenia	[redacted]	[redacted]	NR	NR
Headache	50 (11.5)	51 (11.8)	74 (17.2)	57 (13.1)
Insomnia	27 (6.2)	23 (5.3)	30 (7.0)	25 (5.7)
Cough	37 (8.5)	31 (7.2)	30 (7.0)	29 (6.7)
Rash	25 (5.7)	18 (4.2)	30 (7.0)	28 (6.4)
Lymphadenopathy	NR	NR	[redacted]	[redacted]
Constipation	NR	NR	[redacted]	[redacted]
Dizziness	NR	NR	[redacted]	[redacted]
Anxiety	NR	NR	[redacted]	[redacted]
Oropharyngeal pain	NR	NR	[redacted]	[redacted]
SAEs				
Patients with > 0 SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs				
WDAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths				
Number of deaths, n (%)	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.5)

AE = adverse event; COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; NR = not reported; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Note: "NR" may include events that occur at a frequency < 5%.
Source: Study 104 Clinical Study Report (CSR),[2] study 111 CSR.[3]

TABLE 23: HARMS — VIROLOGICALLY SUPPRESSED ADULTS (RANDOMIZED CONTROLLED TRIALS, FREQUENCY > 5%)

	Study 109		Study 1089	
	EVG/COBI /FTC/TAF (N = 959)	FTC/TDF +3rd Drug (N = 477)	FTC/TAF + 3rd Drug (N = 333)	FTC/TDF + 3rd Drug (N = 330)
AEs				
Patients with > 0 AEs, n (%)	828 (86.3)	399 (83.7)	281 (84.4)	262 (79.4)
Most common AEs (> 5%), n (%)				
Diarrhea	96 (10.0)	42 (8.8)	30 (9.0)	33 (10.0)
Nausea	50 (5.2)	16 (3.4)	[redacted]	[redacted]
Fatigue	NR	NR	18 (5.4)	13 (3.9)
URTI	151 (15.7)	54 (11.3)	30 (9)	45 (13.6)
Nasopharyngitis	88 (9.1)	39 (8.2)	25 (7.5)	20 (6.1)
Syphilis	46 (4.8)	30 (6.3)	[redacted]	[redacted]
Bronchitis	58 (6.0)	26 (5.5)	21 (6.3)	17 (5.2)
Back pain	52 (5.4)	25 (5.2)	21 (6.3)	15 (4.5)
Arthralgia	59 (6.2)	24 (5.0)	19 (5.7)	9 (2.7)
Osteopenia	56 (5.8)	22 (4.6)	[redacted]	[redacted]
Headache	69 (7.2)	20 (4.2)	27 (8.1)	15 (4.5)
Insomnia	50 (5.2)	30 (6.3)	NR	NR
Cough	64 (6.7)	25 (5.2)	21 (6.3)	16 (4.8)
Depression	42 (4.4)	30 (6.3)	[redacted]	[redacted]
Sinusitis	48 (5.0)	25 (5.2)	[redacted]	[redacted]
SAEs				
Patients with > 0 SAEs, N (%)	65 (6.8)	35 (7.3)	18 (5.4)	14 (4.2)
WDAEs				
WDAEs, N (%)	9 (0.9)	12 (2.5)	7 (2.1)	3 (0.9)
Deaths				
Number of deaths, N (%)	4 (0.4)	0	1 (0.3)	0

AE = adverse event; COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; NR = not reported; SAE = serious adverse event; TAF= tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Note: "NR" may include events that occur at a frequency < 5%.
Source: Mills et al. (2015), [37] Clinical Study Report study 1089,[16] p. 95.

TABLE 24: HARMS – SPECIAL POPULATIONS (OPEN-LABEL SINGLE-ARM, FREQUENCY > 5%)

	Study 112 (Reduced Kidney Function)				Study 106 (Adolescents)
	Switch to EVG/COBI/FTC/TAF			ART-Naive (N = 6)	ART-Naive (N = 48)
	BL $eGFR_{CG}$ < 50 mL/min (N = 80)	BL $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)		
	EVG/COBI/FTC/TAF				EVG/COBI /FTC/TAF
AEs					
Patients with > 0 AEs, n (%)	67 (83.8)	142 (87.7)	209 (86.4)	5 (83.3)	39 (81.3)
Most common AEs (> 5%), n (%)					
Headache	2 (2.5)	15 (9.3)	17 (7.0)	0	7 (14.6)
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	7 (14.6)
Abdominal pain, upper	NR	NR	NR	NR	3 (6.3)
Respiratory tract infection	NR	NR	NR	NR	7 (14.6)
Nausea	5 (6.3)	12 (7.4)	17 (7.0)	0	11 (22.9)
Diarrhea	8 (10.0)	13 (8.0)	21 (8.7)	1 (16.7)	8 (16.7)
URTI	1 (1.3)	16 (9.9)	17 (7.0)	1 (16.7)	10 (20.8)
Vomiting	NR	NR	NR	NR	6 (12.5)
Dizziness	7 (8.8)	7 (4.3)	14 (5.8)	0	5 (10.4)
Vitamin D deficiency	NR	NR	NR	NR	5 (10.4)
Renal cyst	5 (6.3)	8 (4.9)	13 (5.4)	0	NR
Cough	4 (5.0)	8 (4.9)	12 (5.0)	0	NR
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	NR
Fatigue	4 (5.0)	10 (6.2)	14 (5.8)	1 (16.7)	NR
Bronchitis	7 (8.8)	12 (7.4)	19 (7.9)	0	NR
Arthralgia	6 (7.5)	14 (8.6)	20 (8.3)	1 (16.7)	NR
Osteopenia	[redacted]	[redacted]	[redacted]	[redacted]	NR
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	NR
Back pain	2 (2.5)	13 (8.0)	15 (6.2)	0	NR
Body tinea	NR	NR	NR	NR	4 (8.3)
Bronchopneumonia	NR	NR	NR	NR	4 (8.3)
Upper tract infection	NR	NR	NR	NR	3 (6.3)
Somnolence	NR	NR	NR	NR	3 (6.3)
Rash popular	NR	NR	NR	NR	3 (6.3)
SAEs					
Patients with > 0 SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	4 (8.3)
WDAEs					
WDAEs, n (%)	6 (7.5)	2 (1.2)	8 (3.3)	0	0
Deaths					
Number of deaths, n (%)	0	0	0	0	0

AE = adverse event; ART = antiretroviral therapy; BL = baseline; COBI= cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FTC = emtricitabine; NR = not reported; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Note: "NR" may include events that occur at a frequency < 5%.
Source: Study 112 Clinical Study Report (CSR),[4] study 106 CSR.[5]

TABLE 25: NOTABLE HARMS (BONE AND RENAL SYSTEMS) —TREATMENT-NAIVE ADULTS (RANDOMIZED CONTROLLED TRIALS)

		Study 104		Study 111	
		EVG/COBI/FTC/TAF	EVG/COBI/FTC/TDF	EVG/COBI/FTC/TAF	EVG/COBI/FTC/TDF
$eGFR_{CG}$ (mL/min)					
Baseline (mL/min)	**N**				
	Median (Q1, Q3);				
	***P* value**				
Change at week 48	**N**				
	Median (Q1, Q3)				
	***P* value**				
Hip BMD[a]					
Baseline (g/cm^2)	**N**				
	Mean (SD)				
	Difference in LSM (95% CI); *P* value				
% Change at week 48	**N**				
	Mean (SD)				
	Difference in LSM (95% CI); *P* value				
Spine BMD[a]					
Baseline (g/cm^2)	**N**				
	Mean (SD)				
	Difference in LSM (95% CI); *P* value				
% Change at week 48	**N**				
	Mean (SD)				
	Difference in LSM (95% CI); *P* value				

BMD = bone mineral density; CI = confidence interval; COBI = cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; DXA = Dual X-ray absorptiometry; EVG = elvitegravir; FTC = emtricitabine; LSM = least squares mean; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

[a] Using DXA analysis sets.

Source: Study 104 Clinical Study Report (CSR),[2] study 111 CSR.[3]

TABLE 26: NOTABLE HARMS (BONE AND RENAL SYSTEMS) — VIROLOGICALLY SUPPRESSED ADULTS (RANDOMIZED CONTROLLED TRIALS)

		Study 109		Study 1089	
		EVG/COBI/FTC/TAF	FTC/TDF +3rd Drug	FTC/TAF +3rd Drug	FTC/TDF +3rd Drug
$eGFR_{CG}$ (mL/min)					
Baseline (mL/min)	**N**	708	352	[redacted]	[redacted]
	Median (Q1, Q3)	103.8 (87.7 to 120.9)	102.4 (84.4 to 121.5)	[redacted]	[redacted]
	***P* value**	0.55		[redacted]	
Change at week 48	**N**	545	265	[redacted]	[redacted]
	Median (Q1, Q3)	1.8 (–6.6 to 9.7)	–3.7 (–11.1 to 3.6)	8.4 (0.2 to 15.6)	2.8 (–5.1 to 10.9)
	***P* value**	*P* < 0.001		*P* < 0.001	
Hip BMD[a]					
Baseline (g/cm^2)	**N**	NR	NR	321	317
	Mean (SD)	NR	NR	[redacted]	[redacted]
	Difference in LSM (95% CI); *P* value	NR		[redacted]	
% Change at week 48	**N**	869	428	[redacted]	[redacted]
	Mean (SD)	1.5 (2.7)	–0.3 (2.8)	1.1 (2.8)	–0.2 (2.5)
	Difference in LSM (95% CI); *P* value	1.8 (1.5 to 2.1); *P* < 0.0001		[redacted]	
Spine BMD[a]					
Baseline (g/cm^2)	**N**	NR	NR	321	320
	Mean (SD)	NR	NR	[redacted]	[redacted]
	Difference in LSM (95% CI); *P* value	NR		[redacted]	
% Change at week 48	**N**	881	436	[redacted]	[redacted]
	Mean (SD)	1.6 (3.8)	–0.4 (4.1)	1.5 (3.2)	–0.2 (3.2)
	Difference in LSM (95% CI); *P* value	2.0 (1.6 to 2.5); *P* < 0.0001		[redacted]	

BMD = bone mineral density; CI = confidence interval; COBI = cobicistat; DXA = dual X-ray absorptiometry; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FTC = emtricitabine; LSM = least squares mean; NR = not reported; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

[a] Using DXA analysis sets in study 1089. The data analysis set for hip and spine BMD was not clearly described for study 109 (Mills et al. 2016).[37]

Source: Study 109 Clinical Study Report (CSR),[6] ($eGFR_{CG}$ data), Mills et al. 2016[37] (Hip BMD and Spine BMD data); study 1089 CSR.[16]

TABLE 27: NOTABLE HARMS (BONE AND RENAL SYSTEMS) — SPECIAL POPULATIONS (OPEN-LABEL SINGLE-ARM)

		Study 112 (Reduced Kidney Function)				Study 106 (Adolescents)
		Switch to EVG/COBI/FTC/TAF			ART-Naive	ART-Naive
		BL $eGFR_{CG}$ < 50 mL/min	BL $eGFR_{CG}$ ≥ 50 mL/min	Total		
		EVG/COBI/FTC/TAF				EVG/COBI /FTC/TAF
eGFR[a]						
Baseline (mL/min)	**N**	80	162	242	6	[redacted]
	Median (Q1, Q3)	43 [redacted]	60 [redacted]	56 [redacted]	[redacted]	[redacted]
Change at week 24	**N**	76	157	233	6	[redacted]
	Median (Q1, Q3)	1.2 (–3.9 to 5.6)	–0.9 (–4.8 to 3.6)	–0.4 (–4.7 to 4.5)	–0.3 (–3.6 to 1.3)	[redacted]
Hip BMD[b]						
Baseline (g/cm^2)	**N**	NR		236	6	[redacted]
	Mean (SD)			0.918 (0.1554)	0.973 (0.2124)	
% Change at week 24	**N**			225	6	
	Mean (SD)			0.733 (2.7674)	–0.022 (1.6853)	
Spine BMD[b]						
Baseline (g/cm^2)	**N**	NR		236	6	[redacted]
	Mean (SD)			1.1 (0.2)	1.0 (0.2)	[redacted]
	Median (Q1, Q3)			NR	NR	[redacted]
% Change at week 24	**N**			226	6	[redacted]
	Mean (SD)			1.6 (3.6)	–2.7 (4.6)	[redacted]
	Median (Q1, Q3)			NR	NR	[redacted]
TBLH BMD						
Baseline (g/cm^2)	**N**	NR				[redacted]
	Mean (SD)					[redacted]
	Median (Q1, Q3)					[redacted]
% Change at week 24	**N**					[redacted]
	Mean (SD)					[redacted]
	Median (Q1, Q3)					[redacted]

ART = antiretroviral therapy; BL = baseline; BMD = bone mineral density; CI = confidence interval; COBI = cobicistat; DXA = dual X-ray absorptiometry; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FTC = emtricitabine; LSM = least squares mean; NR = not reported; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; TAF = tenofovir alafenamide fumarate; TBLH = total body less head; TDF = tenofovir disoproxil fumarate.

[a] For study 112, eGFR is by Cockcroft–Gault formula (mL/min); for study 106, eGFR is by Schwartz formula ($mL/min/1.73m^2$).

[b] Using DXA analysis sets.

Source: Study 112 Clinical Study Report (CSR),[4] study 106 CSR.[5]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was drawn from six studies [2-6] were reviewed in the CDR submission for EVG/COBI/FTC/TAF (Genvoya). The inclusion of studies evaluating the FTC/TAF-based ART regimen EVG/COBI/FTC/TAF was based on evidence from two bioequivalence studies. These studies were randomized, open-label, single-dose, two-way, crossover phase 1 studies (study 1472[7] and study 1473[8]) that evaluated the bioequivalence of FTC and TAF between: a) FTC/TAF FDC + EVG + COBI[7] or, b) FTC/TAF fixed-dose combination,[8] and EVG/COBI/FTC/TAF. The FTC and TAF components of FTC/TAF + EVG + COBI,[7] or FTC/TAF FDC[8] were found to be bioequivalent to the FTC and TAF components of EVG/COBI/FTC/TAF. The sixth study was not included in the CDR review of EVG/COBI/FTC/TAF.

Among the six included studies, three were phase 3 multi-centre, double-blind, double-dummy, active-controlled non-inferiority trials (study 104, n = 872; study 111, n = 872; study 1089, n = 663); one was a phase 3 multi-centre, open-label, active-controlled non-inferiority trial (study 109, n = 1,443), and two were multi-centre, open-label, single-group cohort studies (study 112, n = 252; study 106, n = 48). The primary efficacy outcome for all studies was the percentage of patients with HIV-1 RNA < 50 copies/mL at week 48 (studies 104, 111, and 109) or week 24 (studies 112 and 106) using the FDA-defined snapshot algorithm.

Studies 104 and 111 exclusively enrolled treatment-naive adults, whereas studies 109 and 1089 enrolled only virologically suppressed adults who had been on an FTC/TDF-based regimen (EVG/COBI/FTC/TDF or FTC/TDF + a third drug). The consulting clinical expert confirmed that the study populations were generally reflective of Canadian practice. Patients with hepatitis B or hepatitis C were excluded from the studies; hence, the data are insufficient or unavailable to determine the relative efficacy and safety of FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) in these populations. Patients with hepatitis B or hepatitis C may have been excluded due to uncertainty regarding the safety and efficacy of FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) in patients coinfected with HIV-1 and hepatitis B, or because of interactions with drugs required for treatment of hepatitis C infection (for example, ledipasvir/sofosbuvir). It is also unknown how the safety and efficacy of multi-tablet FTC/TAF-based regimens (FTC/TAF + a third drug) directly compare with single-tablet regimens available in Canada. Additionally, there was no evidence to assess the comparative safety and efficacy of multi-tablet FTC/TAF and FTC/TDF-based regimens in treatment-naive adults.

Studies 112 and 106 evaluated the efficacy and safety of an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) in HIV-infected adults with mild to moderate kidney impairment (virologically suppressed patients: 97.6%; ART-naive patients: 2.4%) (study 112) and treatment-naive adolescents (study 106). Due to the single-arm design of these studies, no comparative evidence was available. In addition, given the small number of treatment-naive patients enrolled in this study (n = 6), the results were insufficient to draw robust conclusions about the efficacy and safety of EVG/COBI/FTC/TAF in this particular subgroup of patients. Study 106 enrolled only treatment-naive adolescents (12 to 18 years of age) who weighed ≥ 35 kg. Given the small number of patients analyzed (n = 23) for the primary efficacy outcome, it is difficult to draw robust conclusions about the safety and efficacy of FTC/TAF-based regimens in this population. As well, there were no data for treatment-experienced adolescents requiring a switch from existing therapy.

4.2 Interpretation of Results

4.2.1 Efficacy

In studies 104, 111, 109, and 1089, the FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) were non-inferior to FTC/TDF-based regimens (EVG/COBI/FTC/TDF) with respect to the primary efficacy outcome. These results were consistent with pooled data from studies 104 and 111 at 48 weeks[35] and 96 weeks (Appendix 4, Table 32). Furthermore, in study 109, results from the superiority test (FAS) demonstrated that statistically significantly more patients who switched to an FTC/TAF-based regimen (FTC/TAF + a third drug)[16] versus those who stayed on their pre-existing FTC/TDF + third drug regimen achieved HIV-1 RNA < 50 copies/mL at week 48.

In study 112, the primary analysis demonstrated that the virologic success rate at 24 weeks was 95.0% among adult patients who switched to EVG/COBI/FTC/TAF from their existing ARV regimen (97.6% of patients), and was 83.3% for treatment-naive adults (2.4% of patients) who received EVG/COBI/FTC/TAF. However, the results should be interpreted with caution given the non-comparative nature of the data, and the small number of treatment-naive patients enrolled (n = 6). In study 106, the virologic success rate at 24 weeks was 91.3% for 23 ART-naive adolescents receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF). The data for adolescents with HIV infection were non-comparative; only a small number of patients were enrolled (n = 48), and only 23 out of 48 patients were included in the interim analysis. Although the rate of virological suppression in study 106 was similar to the rates observed in the comparative trials in adults, the results should be interpreted with caution due to the limitations mentioned above.

Overall, the consulting clinical expert highlighted that the rates of virologic success across the studies, although quite good, were lower than what is observed in usual clinical practice, likely due to the greater flexibility (in choosing regimens) that clinicians have in treating HIV-infected patients in practice.

Very few patients developed primary genotypic resistance through week 48 in the four RCTs. In studies 112 and 106, through week 48, no patients receiving EVG/COBI/FTC/TAF developed new resistance or resistance-associated mutations that were not already present at baseline.

There were no differences in HRQoL among patients receiving an FTC/TAF-based regimen or an FTC/TDF-based regimen comparator, which is consistent with the expectations from the consulting clinical expert. The submission from patient groups for this review also suggested that there is some variation between patients with respect to the direction of change in HRQoL when patients receive ART.

Across all studies, at least 77% of patients in each treatment arm achieved adherence rates of ≥ 95%.

4.2.2 Harms

Across all six studies, at least 80% of patients in each trial experienced at least one TEAE. Diarrhea (9% to 19%), nausea (< 5% to 23%), URTIs (9% to 17%), and headache (7% to 17%) appeared to be the most common AEs reported by patients receiving FTC/TAF-based regimens. The frequencies of the above-mentioned AEs were similar in both treatment groups, except that more patients receiving FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) experienced headache than those receiving FTC/TDF-based regimens (EVG/COBI/FTC/TDF or FTC/TDF + a third drug). The percentage of patients who experienced an SAE while receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) varied between studies. Across the four RCTs, fewer patients receiving an FTC/TAF-based regimen withdrew due to AEs (0.7% to 0.9%) than those receiving a FTC/TDF-based

regimen (0% to 2.5%) except in study 1089, where more patients receiving a FTC/TAF-based regimen (2.1%) withdrew due to AEs than those receiving a FTC/TDF-based regimen (0.9%).

There were two deaths reported in study 104 (one in each treatment group) and three in study 111 (one in the FTC/TAF-based regimen group). In study 109, four patients who switched to an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from a pre-existing regimen of FTC/TDF + a third drug died. In study 1089, one patient who switched to an FTC/TAF-based regimen from a pre-existing regimen of FTC/TDF + a third drug died; no patients died in the comparator group. None of the reported deaths were considered treatment-related. There were no deaths in studies 112 and 106.

All six studies evaluated the impact of an FTC/TAF-based regimen (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) on kidney function. Evidence suggests that the risk of kidney disease may increase by as much as seven-fold in HIV-infected individuals compared with the general population.[42,43] Moreover, exposure to TDF, as part of a combination ART regimen, has been shown to increase renal toxicity and reduce kidney function in patients with HIV.[15,44-48] According to the consulting clinical expert, reductions in eGFR are observed in about 10% to 15% of patients treated with TDF, but these changes rarely warrant discontinuation of therapy. Treatment-naive patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) had a smaller reduction in kidney function from baseline to week 48 compared with patients receiving an FTC/TDF-based regimen (EVG/COBI/FTC/TDF) in studies 104 and 111 (as measured by a decrease in median $eGFR_{CG}$). In study 109, median $eGFR_{CG}$ increased slightly (1.8 mL/min) from baseline among patients who switched to a FTC/TAF-based regimen (EVG/COBI/FTC/TAF) from a pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug), but decreased (–3.7 mL/min) among those who stayed on their pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug). In study 1089, renal function improved in both treatment arms, with patients in the FTC/TAF-based regimen group (FTC/TAF + a third drug) having a statistically significant improvement in renal function compared with patients in the FTC/TDF-based treatment arm (FTC/TDF + a third drug) (median difference: 5.6 mL/min, $P < 0.001$).

In study 112, among virologically suppressed adults receiving EVG/COBI/FTC/TAF, overall kidney function appeared to decrease at 24 weeks, although the effect seemed to differ by severity of kidney impairment at baseline. The trend for decreased overall kidney function was also evident from baseline to week 24 among treatment-naive adolescents receiving EVG/COBI/FTC/TAF in study 106. The clinical expert involved in this review indicated that the magnitude of the changes in kidney function and the differences between treatment groups across studies were not likely to be clinically meaningful, but may be important in the long term.

HIV-infected individuals experience accelerated bone loss compared with the general population, especially with TDF exposure; however, the risk of fracture is low, according to the consulting clinical expert. In studies 104 and 111, treatment-naive adult patients receiving an FTC/TAF-based regimen (EVG/COBI/FTC/TAF) had a smaller mean percentage reduction in BMD in the hip and spine from baseline to week 48 compared with patients receiving FTC/TDF-based regimens (EVG/COBI/FTC/TDF). This difference was statistically significant in both studies ($P < 0.001$). In studies 109 and 1089, there was a statistically significant increase in per cent change in mean hip and spine BMD from baseline to week 48 in virologically suppressed adult patients who switched to a FTC/TAF-based regimen (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) compared with patients who stayed on their pre-existing FTC/TDF-based regimen (FTC/TDF + a third drug) ($P < 0.0001$ for study 109; $P < 0.001$ for study 1089). In study 112, the overall mean BMD of the hip and spine increased in patients who switched to EVG/COBI/FTC/TAF from their pre-existing ART regimens. The clinical expert involved in this review indicated that the magnitude of the changes (across all studies) in BMD were not likely to be clinically

meaningful, but may be important in the long term. It is noteworthy, however, that Health Canada raised concerns with respect to the harmful effects of EVG/COBI/FTC/TAF on the bone system in adolescents in light of a week 24 interim analysis of study 106 that identified four patients with worsening in the spine or TBLH height-age-adjusted BMD Z-score from baseline. The manufacturer highlighted that three of these patients subsequently showed improvements in BMD at week 48. Consequently, given the small sample size of study 106, the effects of EVG/COBI/FTC/TAF on the bone system in adolescent patients remain uncertain.

4.3 Potential Place in Therapy

The optimal ART is one that suppresses HIV replication completely, promotes adherence, and has no short-term AEs or long-term toxicities. The standard of care for ART for HIV typically consists of a "backbone" of two nucleoside reverse transcriptase inhibitors (NRTIs), which are generally ABC/3TC (Kivexa) or FTC/TDF (Truvada), combined with another antiviral drug (with or without a booster, such as COBI or ritonavir).[9] ABC/3TC is hindered by the requirement for genetic testing for HLA B5701 prior to its use,[10,11] the possibility of reduced effectiveness at higher VLs,[12] and the association in some studies with myocardial infarctions.[13] As such, FTC/TDF is the most commonly used antiviral backbone. FTC/TDF is very well tolerated, but BMD may decline in some patients,[14] and there is some evidence for renal phosphate wasting or renal failure.[15]

FTC/TAF is the newest backbone co-formulation therapy. It achieves lower plasma levels of tenofovir, leading to fewer effects on renal function or BMD, but with effectiveness for suppression of HIV replication similar to that of FTC/TDF. Moreover, there are no expected pharmacokinetic or pharmacodynamic differences between FTC/TAF and FTC/TDF. It is very likely that FTC/TAF will replace FTC/TDF in almost all patients with HIV infection. The exceptions to this would be:

- in patients receiving post-exposure prophylaxis after potential HIV exposure, where the duration of therapy is only 28 days and therefore, the long-term renal and bone toxicities of FTC/TDF would be negligible, and,
- in pre-exposure prophylaxis, where human data documenting the effectiveness of FTC/TAF are unavailable.

Each of the backbone co-formulation therapies (ABC/3TC, FTC/TDF, and FTC/TAF) may be given in combination with another ARV drug as a multi-tablet regimen, or be co-formulated with other ARVs as a single-tablet regimen (EFV/TDF/FTC, FTC/RPV/TDF, EVG/COBI/FTC/TDF, DTG/ABC/3TC, and EVG/COBI/FTC/TAF). Single-tablet regimens are the preferred therapy for the majority of patients given their convenience. However, for patients who have viral resistance, comorbidities, or drug interactions, a multi-tablet regimen may be indicated. As such, according to the clinical expert involved in the review, a fraction of patients, approximately 10% to 15%, will be receiving FTC/TDF as a backbone therapy (in combination with another ARV drug, as opposed to the alternative backbone, ABC/3TC, or a single-tablet regimen), and will be eligible for treatment with FTC/TAF.

5. CONCLUSIONS

The evidence for the efficacy and safety of FTC/TAF-based regimens was based on data from studies that included two formulations: EVG/COBI/FTC/TAF and FTC/TAF + a third drug. The FTC and TAF components in the single-tablet regimen (EVG/COBI/FTC/TAF) were found to be bioequivalent to the FTC and TAF components of FTC/TAF as a fixed-dose combination and FTC/TAF administered simultaneously with EVG and COBI.

FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) were shown to be non-inferior to FTC/TDF-based regimens (EVG/COBI/FTC/TDF or FTC/TDF + a third drug) in suppressing VL among treatment-naive and treatment-experienced adults after 48 weeks of treatment. FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) were associated with relatively similar rates of AEs as FTC/TDF-based regimens in the included studies, among which diarrhea, nausea, URTIs, and headache appeared to be the most common. FTC/TAF-based regimens showed a statistically significant comparative benefit with respect to kidney functioning (eGFR) and bone health (BMD) compared with FTC/TDF-based regimens; however, the observed changes are unlikely to be clinically meaningful in the short term, and are of uncertain importance with respect to the risks of kidney failure and bone fracture in the long term.

There were no comparative efficacy and safety data available for FTC/TAF-based regimens compared with FTC/TDF-based regimens in adult patients with mild to moderate kidney impairment or in adolescents. The clinical efficacy and safety of FTC/TAF-based regimens in these populations are uncertain.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared 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 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 individuals living with HIV (including HCV coinfection) and organizations, groups, or projects with a substantial HIV mandate (including HCV coinfection).

CTAC received unrestricted organizational and educational grants from the following organizations in the 2014–2015 fiscal year: Abbott/AbbVie, Gilead Sciences, Janssen, and ViiV Healthcare. No information was provided regarding whether these conflicts of interest affected the submission.

2. Condition-Related Information

Information was gathered via a national consultation webinar and a survey. The webinar was attended by two participants, but the stakeholder group to whom they belonged (for example, patients, caregivers, or providers) was unclear. The survey was completed by a 33-year old HIV-positive male who indicated having experience with Truvada (for one year), ritonavir, and Prezista. Additional information was collated from survey data used in patient submissions for other HIV treatments, including Stribild, Tivicay, Triumeq, Prezcobix, and Genvoya.

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 of HIV management. For the most part, patients taking HAART achieve viral suppression (an undetectable viral load [VL]), whereby there are fewer than 50 copies/mL in a blood sample. Hence, patients with HIV manage their disease as a chronic illness. However, they often tend to experience "accelerated aging" and become more susceptible to inflammatory and non-infectious comorbidities, such as cardiovascular (CV), kidney, and liver disease, as well as bone fractures.

Patients living with HIV often experience negative mental health outcomes. These can be due to the side effects of treatment or to social stigma, discrimination, and related stress. Mental health issues and stigma were noted by both respondents. One reported that their biggest challenge was regarding the "ignorance about HIV and healthy living and stigma attached to infection," while the other stated, "I was quite depressed and suicidal early on in my infection, and my caregivers had to deal with this." 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 difficulties associated with the disease and accessing treatment. For instance, access to affordable treatment remains difficult for many patients, as are the complications associated with access to treatment when moving between provinces. Also, because HIV treatment tends to be multifaceted — often involving collaboration between different specialists, adherence programs, and outreach programs — stress is often compounded when trying to obtain proper care. To this end, the respondent receiving emtricitabine/tenofovir alafenamide fumarate (FTC/TAF) highlighted the logistical challenges

of receiving treatment for HIV by identifying that "travel costs are the major challenge I face in getting to my appointments." Indeed, flexible work hours are a necessity for many patients and their caregivers, thus compounding the social stigma and stress associated with having and treating HIV.

Caregivers can be negatively affected in many ways. They are often responsible for, or aid in, the travel associated with treatment. Caregivers 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) who ensure adherence to medication. In addition, the peace of mind of the caregivers can be negatively affected when they see their loved ones experiencing treatment side effects, and must constantly encourage them to adhere to their treatment regimen.

3. Current Therapy-Related Information

The survey respondent who indicated receiving Truvada was pleased with the way his treatment quickly (one month) helped him achieve undetectable status, while he did not experience any side effects. He highlighted the impact of the success of his treatment on other aspects of his life as well, specifically commenting that "my quality of life has improved greatly; my energy level has increased as well as my ability to sustain relationships, as I am not afraid of transmission."

Both advantages and challenges were reported by the patients who responded to the previous Stribild, Tivicay, Triumex, and Prezcobix surveys. "Minor" adverse events (AEs) were noted by one patient taking darunavir, while cardiovascular events (including a stroke), gum disease, lipodystrophy, and fatigue were reported by a patient taking a Viramune and a Truvada-based regimen. On ritonavir, one patient reported experiencing gastrointestinal (GI) events such as GI distress, including diarrhea, gas, and weight gain. When adding darunavir to ritonavir, another patient reported high cholesterol and loose stools. One patient taking Complera reported fatigue and a "big stomach," while one patient on Isentress for a four-year period reported a feeling of "wasting" as a side effect.

While all of these side effects affect the patient, some also state that, in addition to the low VLs, they have "less fear of catching opportunistic infections." One noted that there were still challenges associated with their rehabilitation from sickness to health and subsequent return to work, but that their quality of life (QoL) had improved. Another patient reported no change in QoL, while another patient reported a decrease, stating, "…I'm more depressed than I used to be."

Treatment adherence (specifically, taking the medication when and as prescribed) is particularly important with regard to HIV treatment, as non-adherence can lead to drug-class resistance. Once this occurs, it is necessary for the patient to embark on a different treatment regimen. Therefore, patients and patient groups note that having many options available is of the utmost clinical importance.

4. Expectations About the Drug Being Reviewed

CTAC believes that having a maximum number of possible treatment options is of great clinical importance, not only due to obtaining sufficiently low VLs, but also in the case of adherence issues.

The survey respondent who indicated receiving Truvada was enthusiastic about the long-term benefits of FTC/TAF, and would consider switching to FTC/TAF from his current FTC/tenofovir disoproxil fumarate (TDF) regimen, as "if it is less harmful over long periods, it would improve my health in my later years." The individual expected that the safety profiles of FTC/TAF and FTC/TDF would be similar, and anticipated that his health outcomes after years of HIV treatment "would improve, as I would have less worry about complications later in my life."

From the Genvoya consultation, one respondent was uninterested in switching to Genvoya (from the current treatment regimen) due to the perceived challenges associated with a new treatment, while the other would only do so on the advice of his Infectious Diseases specialist, as this individual felt there was "no compelling reason to change to another therapy when the one I am on is effective and has a better safety profile than previous therapies." Both suspected that their QoL would be the same on the elvitegravir/cobicistat/ (EVG/COBI)/TDF/TAF regimen as it is on their current therapy.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 29, 2016
Alerts:	Bi=weekly search updates until July 20, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt .po	Publication type Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
Line #	**Search Strategy**	**Results**
1	(descovy or "FTC/TAF" or "F/TAF" or "emtricitabine/tenofovir alafenamide").ti,ab,kf.	27
2	143491-57-0.rn,nm.	5588
3	(emtricitabin* or emtriva* or coviracil* or racivir* or Hui Er Ding* or Xin Luo Shu* or 524W91 or "BW 1592" or "BW 524 w 91" or "BW 524 W91" or "BW 524W" or BW524W or BW524W91 or "DRG 0208" or DRG0208 or "psi 5004" or psi5004 or "HSDB 7337" or HSDB7337 or G70B4ETF4S or dOTFC or FTC).ti,ab,ot,hw,kf,rn,nm.	14890
4	2 or 3	14891
5	(379270-37-8 or 377091-31-1 or 147127-20-6 or "GS 7340" or GS7340 or EL9943AG5J or TAF).ti,ab,ot,kf,hw,rn,nm.	12958
6	(tenofovir adj2 alafenamide).ti,ab,kf.	105
7	5 or 6	12976
8	4 and 7	4420
9	8 use pmez	14
10	*emtricitabine/	630
11	(emtricitabin* or emtriva* or coviracil* or racivir* or Hui Er Ding* or Xin Luo Shu* or 524W91 or "BW 1592" or "BW 524 w 91" or "BW 524 W91" or "BW 524W" or BW524W or BW524W91 or "DRG 0208" or DRG0208 or "psi 5004" or psi5004 or "HSDB 7337" or HSDB7337 or G70B4ETF4S or dOTFC or FTC).ti,ab.	8167
12	10 or 11	8337
13	*tenofovir alafenamide/	41
14	("GS 7340" or GS7340 or EL9943AG5J or TAF or 379270-37-8 or 377091-31-1 or 147127-20-6).ti,ab,kw.	2155
15	(tenofovir adj2 alafenamide).ti,ab,kw.	106
16	13 or 14 or 15	2191
17	12 and 16	49
18	17 use oemezd	37
19	1 or 9 or 18	54
20	remove duplicates from 19	42
21	20 not conference abstract.pt.	17

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	February 2016
Keywords:	Emtricitabine/tenofovir alafenamide
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
None	Not available

APPENDIX 4: ADDITIONAL DATA

Drug Exposure

TABLE 28: DURATION OF EXPOSURE TO STUDY DRUG IN TREATMENT-NAIVE ADULTS (SAFETY ANALYSIS SET)

Total Exposure to Study Drug[a,b]	Study 104		Study 111	
	EVG/COBI/FTC/TAF (N = 435)	EVG/COBI/FTC/TDF (N = 432)	EVG/COBI/FTC/TAF (N = 431)	EVG/COBI/FTC/TDF (N = 435)
Mean (SD), weeks	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 16 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 24 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 36 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 48 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 60 weeks, n, (%))	[redacted]	[redacted]	[redacted]	[redacted]
≥ 72 weeks, n, (%))	[redacted]	[redacted]	[redacted]	[redacted]

COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; TAF= tenofovir alafenamide fumarate; SD = standard deviation; TDF = tenofovir disoproxil fumarate.

[a] Duration of exposure to study drugs was the number of weeks between the first and last dose of study drug.

[b] If the last dose date was completely missing, or if only the year was known, or a patient was still on the study drug, the latest of the study drug's start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date; in case of the last study drug, if end data were non-missing, then it was used to impute the last dose date.

Source: Study 104 Clinical Study Report (CSR),[2] study 111 CSR. [3]

TABLE 29: DURATION OF EXPOSURE TO STUDY DRUG IN VIROLOGICALLY SUPPRESSED ADULTS (SAFETY ANALYSIS SET)

Exposure to Study Drug	Study 109		Study 1089	
	EVG/COBI/FTC/TAF (N = 959)	FTC/TDF + 3rd Drug (N = 477)	FTC/TAF + 3rd Drug (N = 333)	FTC/TDF + 3rd Drug (N = 330)
Mean (SD)				
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 24 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 36 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 48 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 60 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 72 weeks	[redacted]	[redacted]	[redacted]	[redacted]

COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; SD = Standard deviation; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

Source: Study 109 Clinical Study Report (CSR),[6] study 1089 CSR.[16]

TABLE 30: DURATION OF EXPOSURE TO STUDY DRUG IN SPECIAL POPULATIONS (SAFETY ANALYSIS SET)

	Study 112				Study 106 (Adolescents)
	Cohort 1: Switch			Cohort 2: ART-Naive	ART-Naive
	BL $eGFR_{CG}$ < 50 mL/min	BL $eGFR_{CG}$ ≥ 50 mL/min	Total		
	EVG/COBI/FTC/TAF				EVG/COBI/FTC/TAF
Total Exposure to Study Drug (weeks)					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 24 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 36 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 48 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 60 weeks, n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ART = antiretroviral therapy; BL = baseline; COBI = cobicistat; $eGFR_{cg}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FTC = emtricitabine; NR = not reported; SD = standard deviation; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

Note: Duration of exposure to study drug was the number of weeks between the first and last dose of the study drug. The latest of study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date for patients with the last dose date completely missing, with only the year known, or for patients still on study drug. If the end date of the last record of study drug was available, then it was used to impute the last dose date.

Source: Study 112 Clinical Study Report (CSR),[4] and study 106 CSR.[5]

TABLE 31: BASELINE THIRD ANTIRETROVIRAL DRUGS IN STUDIES 109 AND 1089

	Study 109		Study 1089	
	EVG/COBI/FTC/TAF (N = 959)	FTC/TDF + 3rd Drug (N = 477)	F/TAF + 3rd Drug (N = 333)	FTC/TDF + 3rd Drug (N = 330)
Baseline third Drug n (%)				
ATV/r[a]	Yes	Yes	53 (15.9)	50 (15.2)
DRV/r[a]	-	-	84 (25.2)	82 (24.8)
LPV/r[a]	-	-	18 (5.4)	18 (5.5)
DTG	-	-	26 (7.8)	23 (7.0)
EFV	Yes	Yes	8 (2.4)	6 (1.8)
[redacted]	-	-	[redacted]	[redacted]
[redacted]	-	-	[redacted]	[redacted]
RAL	-	-	66 (19.8)	73 (22.1)
[redacted]	-	-	[redacted]	[redacted]
[redacted]	Yes	Yes	[redacted]	[redacted]
[redacted]	Yes (co-formulated, single-tablet regimen)	Yes (co-formulated, single-tablet regimen)	[redacted]	[redacted]

ARV = antiretroviral; ATV/r = ritonavir-boosted atazanavir; COBI = cobicistat; EFV = efavirenz; DRV/r = ritonavir-boosted darunavir; EVG = elvitegravir; FTC = emtricitabine; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.
Note: n (%) for the baseline ARV drugs were not provided in the Clinical Study Report for study 109.
[a] TAF 10 mg was used in ART regimens that included protease inhibitors boosted with cobicistat or ritonavir. TAF 25 mg was used in all other ART regimens.
Source: Study 1089 Clinical Study Report (CSR),[16] study 109 CSR.[6]

TABLE 32: ADDITIONAL EFFICACY OUTCOMES — TREATMENT-NAIVE ADULTS (RANDOMIZED CONTROLLED TRIALS, WEEK 96)

		Study 104 and Study 111[a]		Study 109	
Virologic success (snapshot analysis), week 96		EVG/COBI/FTC/TAF (N = 866)	EVG/COBI/FTC/TDF (N = 867)	EVG/COBI/FTC/TAF	FTC/TDF + 3rd Drug
Overall Population				[redacted]	
HIV-1 RNA < 50 copies/mL, n (%)	FAS	[redacted]	[redacted]		
	PP	[redacted]	[redacted]		
Difference in % (95.002% CI); *P* value	FAS	[redacted]			
	PP	[redacted]			
By VL Subgroup					
≤ 100,000 copies/mL		[redacted]	[redacted]		
Difference in % (95% CI); *P* value		[redacted]			
> 100,000 copies/mL		[redacted]	[redacted]		
Difference in % (95% CI); *P* value		[redacted]			

CI = confidence interval; COBI = cobicistat; EVG = elvitegravir; FAS = full analysis set; FTC = emtricitabine; PP = per-protocol analysis set; RNA = ribonucleic acid; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; VL = viral load.
Note: FAS unless otherwise specified.
[a] Data presented are based on the pooled analysis of study 104 and study 111.
Source: Data presented in Table 32 were extracted from the contents of a manufacturer's response to a request for additional information dated March 23, 2016.[49]

TABLE 33: ADDITIONAL EFFICACY OUTCOMES – SPECIAL POPULATIONS (OPEN-LABEL SINGLE-GROUP, WEEK 48)

	Study 112				Study 106 (Adolescents)
Virologic success (snapshot analysis), Week 48	Switch to EVG/COBI/FTC/TAF			ART-Naive	ART-Naive
	BL $eGFR_{CG}$ < 50 mL/min	BL $eGFR_{CG}$ ≥ 50 mL/min	Total		
	EVG/COBI/FTC/TAF				EVG/COBI/FTC/TAF
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HIV-1 RNA < 50 copies/mL, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	

ART = antiretroviral therapy; BL = baseline; COBI = cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; EVG = elvitegravir; FTC = emtricitabine; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.
Source: Study 112 Clinical Study Report (CSR),[4] study 106 CSR[5]

APPENDIX 5: RESISTANCE DATA

Information from studies 104, 111, 109, 112, and 106 in this section were taken verbatim from the contents of a manufacturer's response to a request for additional information dated March 23, 2016.[49] Note: In some cases, drug names (e.g., Genvoya) were replaced by their components (e.g., elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate [EVG/COBI/FTC/TAF]) to match the terminology used throughout the report.

TABLE 34: RESISTANCE THROUGH WEEK 48 IN STUDIES 104 AND 111 COMBINED

		EVG/COBI/FTC/TAF (n = 866)	EVG/COBI/FTC/TDF (n = 867)
Patients analyzed for resistance		16 (1.8)	19 (2.2)
Primary Genotypic Resistance	Any, n (%)	7 (0.8)	5 (0.6)
	Study 104, n	3	3
	Study 111, n	4	2
NRTI Resistance, n	Any, n	7	5
	M184V/I	6	3
	M184V/I + K65R	1	2
INSTI Resistance, n	Any, n	5	3
	T66A	1	0
	E92Q	2	1
	N155H	1	0
	Q148R	0	1
	Q148R + T66I/A	1	0
	Q148R + E92Q	0	1

COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand-transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.
Source: Data presented in Table 34 were taken from contents of a manufacturer's response to a request for additional information dated March 23, 2016.[49]

Study 109

Resistance through week 48: Of total 959 patients in the EVG/COBI/FTC/TAF switch arm, 10 patients developed virologic failure, with one having resistance to FTC (M184M/I). Of total 477 patients in the FTC/TDF-based regimen arm, there were six patients who developed virologic failure, with no documented cases of resistance to study drug.[49] In study 1089, [redacted] patient in the FTC/TAF + third agent group had resistance mutations emerge ([redacted] Table 35).

TABLE 35: STUDY 1089: HIV-1 GENOTYPIC RESISTANCE THROUGH WEEK 48

Resistance Category	Number of Subjects n (%)		
	FTC/TAF + 3rd Agent (n = 333)	FTC/TDF + 3rd Agent (n = 330)	*P* Value[a]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
M184V/I	1 (0.3)	0	1.0
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

FTC/TAF = emtricitabine/tenofovir alafenamide fumarate; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; INSTI-R = primary integrase strand inhibitor resistance; NRTI-R = nucleoside/nucleotide reverse transcriptase inhibitor resistance; NNRTI-R = non-nucleoside reverse transcriptase inhibitor resistance; PI-R = primary protease inhibitor resistance; RAP = resistance analysis population; RNA = ribonucleic acid.

[a] Fisher's exact test comparing the proportions in each group using the whole population as the denominator.

[b] No change from pro-viral baseline genotype at NRTI-R, NNRTI-R, primary PI-R, or primary INSTI-R sites using the Monogram Biosciences GenoSure Archive Assay.

[c] NRTI-R mutations are: M41L, E44D, A62V, K65R, D67N, T69D, T69 insertions; K70E/R, L74V/I, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, and K219Q/N/E/R in RT.

[d] NNRTI-R mutations are: V90I, A98G, L100I, K101E/H/P, K103N/S, V106M/A/I, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, and M230L/I in RT.

[e] PI-R mutations are: D30N, V32I, L33F, M46I/L, I47V/A, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/T/S/L, I84V, N88S, and L90M in PR.

[f] INSTI-) mutations are: T66I/A/K, E92Q/G, T97A, Y143R/H/C, S147G, Q148H/K/R, and N155H/S in integrase.

[g] In the F/TAF + third Agent group, Subject 0991-1182 had NNRTI-R mutations detected at week 36 visit and resuppressed to HIV-1 RNA < 50 copies/mL at week 48 while maintaining study drugs. All NNRTI-R mutations were present at baseline.

[h] In the FTC/TDF +third agent group, Subject 2704-1070 had a primary and secondary PI-R mutation detected at week 36 visit and resuppressed to HIV-1 RNA < 50 copies/mL at week 48 while maintaining study drugs. These PI mutations were confirmed to pre-exist upon retrospective analysis of an historical genotype.

Source: Study 1089 Clinical Study Report,[16] and Gallant et., 2016[38]

Study 112

Resistance through week 48: Of a total of 242 patients, three patients experienced virologic failure; however, none of the three patients who failed had new resistance or mutations that were not already present at baseline. The first of these three patients had HIV-1 ribonucleic acid (RNA) < 50 copies/mL on EVG/COBI/FTC/TAF prior to switching to a new regimen; the second patient who had HIV-1 RNA < 400 copies/mL on EVG/COBI/FTC/TAF demonstrated NRTI and PI resistance mutations, which were identical to a pre-study historical genotype; and the third patient took additional antiretrovirals (RPV /FTC/TDF) through day 67 (protocol violation) but was maintained on EVG/COBI/FTC/TAF alone with HIV-1 RNA < 50 copies/mL through week 48 after the protocol violation was discovered.[4939]

Study 106

Resistance through week 24: Of a total 23 patients, n = 2 patients experienced virologic failure, with no documented cases (n = 0) of resistance to study drug.[49]

APPENDIX 6: SUMMARY OF BIOEQUIVALENCE STUDIES

Objective

To summarize the results of two randomized, open-label, single-dose, two-way, crossover phase 1 studies — study 1472 and study 1473 — that evaluated the bioequivalence of emtricitabine (FTC) and tenofovir alafenamide fumarate (TAF) between FTC/TAF fixed-dose combination plus elvitegravir (EVG) plus cobicistat (COBI) (FTC/TAF FDC+ EVG + COBI[7]) or FTC/TAF fixed-dose combination[8] and EVG/COBI/FTC/TAF.

Description of Studies

Study 1472 and 1473 were similarly designed trials (Table 36). Both studies featured an open-label, two-way, crossover phase 1 design. Study 1472 and 1473 randomized 100 and 116 participants, respectively, all of whom were [redacted], aged [redacted] to [redacted] years, who were [redacted], and [redacted]. Both studies lasted for [redacted], which included a [redacted], and a [redacted].

TABLE 36: DETAILS OF STUDIES 1472 AND 1473

		Study 1472	Study 1473
DESIGNS & POPULATIONS	**Study Design**	Open-label, single-dose, two-way, crossover, phase 1 RCT	
	Locations	United States	
	Randomized (N)	100 (50 in each sequence)	116 (58 in each sequence)
	Main inclusion criteria	[redacted]	
	Main exclusion criteria	[redacted]	
DRUGS	**Intervention**	FTC/TAF (200 mg/10 mg) FDC tablet + EVG (150 mg) + COBI (150 mg)	FTC/TAF (200 mg/25 mg)
	Comparator	EVG/COBI/FTC/TAF (150 mg/150 mg/200 mg/10 mg)	
DURATION	**Treatment**	[redacted]	

ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; COBI = cobicistat; ECG = electrocardiogram; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft–Gault formula; FTC = emtricitabine; EVG = elvitegravir; FDC = fixed-dose combination; HBV = hepatitis B virus; HCV = hepatitis C virus; RCT = randomized controlled trial; TAF = tenofovir alafenamide fumarate.
Source: Study 1472 Clinical Study Report (CSR),[7] Study 1473 CSR.[8]

Populations

In study 1472, the [redacted] of participants were [redacted] ([redacted]%) and [redacted] ([redacted]%) (Table 37). At baseline, the mean (standard deviation [SD]) age was [redacted] ([redacted]), mean (SD) BMI was [redacted] ([redacted]), and mean (SD) creatinine clearance was [redacted] ([redacted]). In study 1473, the [redacted] of participants were [redacted] ([redacted]%) and [redacted] ([redacted]%) (Table 37). At baseline, the mean (SD) age was [redacted] ([redacted]), mean (SD) BMI was [redacted] ([redacted]), and mean (SD) creatinine clearance was [redacted] ([redacted]).

TABLE 37: SUMMARY OF BASELINE CHARACTERISTICS

	Study 1472			Study 1473		
	AB[a] (N = 50)	BA[a] (N = 50)	Total (N = 100)	AB[b] (N = 58)	BA[b] (N = 58)	Total (N = 116)
Age (y)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Height (cm)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR$_{CG}$ (mL/min)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

BMI = body mass index; eGFR$_{CG}$ = estimated glomerular filtration rate by Cockcroft–Gault formula; SD = standard deviation.
[a]Treatment A=FTC/TAF (200/10 mg) + EVG (150 mg) + COBI (150 mg); Treatment B=EVG/COBI/FTC/TAF (150/150/200/10 mg). Sequence AB received treatment A on day 1 and treatment B on day 7. Sequence BA received treatment B on day 1 and treatment A on day 7.
[b]Treatment A=FTC/TAF (200/25 mg); Treatment B=EVG/COBI/FTC/TAF (150/150/200/10 mg).
Source: Study 1472 Clinical Study Report (CSR),[7] study 1473 CSR.[8]

Interventions
Study 1472 assessed FTC/TAF (200 mg/10 mg) fixed-dose combination administered with EVG (150 mg) and COBI (150 mg) versus EVG/COBI/FTC/TAF (150 mg/150 mg/200 mg/10 mg) (Table 36).

Study 1473 evaluated FTC/TAF (200 mg/25 mg) versus EVG/COBI/FTC/TAF (150 mg/150 mg/200 mg/10 mg).

Outcomes
Across both studies, the following plasma pharmacokinetic (PK) parameters were calculated for all participants with evaluable PK profiles:

- C_{max}: maximum observed plasma/serum concentration of drug
- T_{max}: time (observed time point) of C_{max}
- λ_z: terminal elimination rate constant
- C_{last}: last observed quantifiable plasma/serum concentration of the drug
- T_{last}: time (observed time point) of C_{last}
- $t_{1/2}$: estimate of the terminal elimination half-life of the drug in plasma/serum
- AUC_{last}: area under the plasma concentration versus time curve from time zero to the last quantifiable concentration
- AUC_{inf}: area under the plasma concentration versus time curve extrapolated to infinite time
- AUC_{exp} %: percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
- V_z/F: apparent volume of distribution of the drug
- CL/F: apparent oral clearance after administration of the drug

A parametric analysis of variance (ANOVA) using a mixed-effects model was fitted to the natural logarithmic transformation of three parameters: AUC_{inf}, AUC_{last}, and C_{max}. The model included the treatment, the treatment sequence, and the period as fixed effects, and the participant within sequence as a random effect. Two-sided 90% confidence intervals (CIs) were constructed for the ratios of geometric least squares means (GLSMs) of these parameters for TAF and FTC only. Bioequivalence was concluded if the CIs were contained within the boundary of 80% to 125%. This boundary is consistent with Health Canada's guidance on determining bioequivalence.[50] The Two One-sided Test method was used with a 5% significant level for each test. There were no adjustments for multiplicity.

Both studies also evaluated safety outcomes, including adverse events (AEs), serious adverse events (SAEs), deaths, and withdrawals due to adverse events (WDAEs).

Pharmacokinetics
In study 1472, the median T_{max} for TAF was 1.50 hours following FTC/TAF + EVG + COBI and 1.00 hours following EVG/COBI/FTC/TAF. Further, the median T_{max} for FTC was 2.02 hours following FTC/TAF + EVG + COBI and 2.00 hours following EVG/COBI/FTC/TAF.

In study 1473, the median T_{max} for TAF was the same (1.50 hours) in both treatment groups. Further, the median T_{max} for FTC was 2.00 hours following administration of FTC/TAF (200 mg/25 mg) versus 3.00 hours following administration of EVG/COBI/FTC/TAF.

Results of the statistical comparisons of the three parameters that were fitted using a mixed-effects model — AUC_{inf}, AUC_{last}, and C_{max} — are presented in Table 38.

TABLE 38: STATISTICAL COMPARISONS OF SELECT TAF AND FTC PHARMACOKINETIC PARAMETERS BETWEEN TREATMENT GROUPS

	Study 1472		Study 1473	
	FTC/TAF (200 mg/ 10 mg) + EVG (150 mg) + COBI (150 mg) [Test]	EVG/COBI/FTC/TAF (150 mg/ 150 mg/200 mg/ 10 mg) [Reference]	FTC/TAF (200 mg/ 25 mg) [Test]	EVG/COBI/FTC/TAF (150 mg/ 150 mg/200 mg/ 10 mg) [Reference]
TAF PK Parameter				
AUC_{last} (h*ng/mL)				
N	[redacted]	[redacted]	116	116
Mean (% CV)	[redacted]	[redacted]	374.0 (43.4)	369.3 (40.6)
GLSM ratio[a] (90% CI)	97.96 (94.69 to 101.34)		100.32 (96.48 to 104.31)	
AUC_{inf} (h*ng/mL)				
N	[redacted]	[redacted]	95	97
Mean (% CV)	[redacted]	[redacted]	396.4 (42.6)	389.5 (39.3)
GLSM ratio[a] (90% CI)	98.34 (94.81 to 101.99)		98.54 (94.61 to 102.62)	
C_{max} (ng/mL)				
N	[redacted]	[redacted]	116	116
Mean (% CV)	[redacted]	[redacted]	280.5 (62.9)	267.8 (59.8)
GLSM ratio[a] (90% CI)	96.86 (89.36 to 104.99)		103.63 (95.46 to 112.49)	
FTC PK Parameter				
AUC_{last} (h*ng/mL)				
N	[redacted]	[redacted]	116	116
Mean (% CV)	10,159.2 (17.2)	10,086.8 (15.9)	9,423.9 (19.3)	10,475.3 (19.7)
GLSM ratio[a] (90% CI)	99.84 (98.41 to 101.29)		90.01 (88.88 to 91.16)	
AUC_{inf} (h*ng/mL)				
N	97	99	116	116
Mean (% CV)	10,535.1 (27.0)	10,294.4 (15.8)	9,654.6 (19.3)	10,706.6 (19.6)
GLSM ratio[a] (90% CI)	100.67 (98.24 to 103.16)		90.20 (89.06 to 91.35)	
C_{max} (ng/mL)				
N	97	99	116	116
Mean (% CV)	1,660.8 (20.6)	1,662.6 (19.1)	1,577.4 (26.8)	1,601.7 (19.6)
GLSM ratio[a] (90% CI)	99.57 (96.78 to 102.44)		97.26 (94.57 to 100.03)	

% CV = coefficient of variation; AUC_{inf} = area under the plasma concentration versus time curve extrapolated to infinite time; AUC_{last} = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed plasma/serum concentration of drug; COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; GLSM = geometric least squares mean; PK = pharmacokinetic; TAF = tenofovir alafenamide fumarate.
[a] GLSM ratio calculated as Test/Reference.
Source: Study 1472 Clinical Study Report (CSR),[7] study 1473 CSR.[8]

Across the studies, the GLSM ratios and corresponding 90% CIs of AUC_{last}, AUC_{inf}, and C_{max} for TAF and FTC were contained within the 80% to 125% boundary criteria pre-specified for bioequivalence (Table 38).

Conclusions

Across both studies, the FTC and TAF components of FTC/TAF fixed-dose combination or FTC/TAF administered simultaneously with EVG and COBI (FTC/TAF + EVG + COBI) appeared to be bioequivalent to the FTC and TAF components of EVG/COBI/FTC/TAF FDC.

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