CADTH

CADTH Common Drug Review

Clinical Review Report

Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/FTC/TAF) (Biktarvy)

(Gilead Sciences Canada, Inc.)

Indication: A complete regimen for the treatment of HIV-1 infection in adults with no known substitution associated with resistance to the individual components of Biktarvy.

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Abbreviations

3TC	lamivudine
B	bictegravir
AE	adverse event
ABC	Abacavir
ANOVA	analysis of variance
ART	antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
BMD	bone mineral density
CDR	CADTH Common Drug Review
CI	confidence interval
C or COBI	cobicistat
DHHS	US Department of Health and Human Services
DRV	Darunavir
DTG	dolutegravir
DXA	dual energy X-ray absorptiometry
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDC	fixed-dose combination
FTC	emtricitabine
HIV-1	HIV type 1
HRQoL	health-related quality of life
IDMC	Independent Data Monitoring Committee
INSTI	Integrase strand transfer inhibitor
IQR	interquartile range
MCS	mental component summary
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PCS	physical component summary
PI	protease inhibitor
PP	per-protocol
RCT	randomized controlled trial
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SBR	stay on baseline regimen
SD	standard deviation
SF-36	Short Form (36) Health Survey
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
WDAE	withdrawal due to adverse event

Drug	Bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF) (BIKTARVY)
Indication	A complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults with no known substitution associated with resistance to the individual components of Biktarvy.
Reimbursement Request	As per indication
Dosage Form(s)	Fixed-dose combination, single-tablet regimen of bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg.
NOC Date	July 10, 2018
Manufacturer	Gilead Sciences Canada, Inc.

Executive Summary

Introduction

Human immunodeficiency virus is the virus responsible for causing HIV infection.[1] HIV is transmitted by infected body fluids such as blood, semen, fluid from the rectum, fluid from the vagina, and breast milk.[2] Based on surveillance data, the Public Health Agency of Canada estimates that, at the end of 2014, there were approximately 75,500 people in Canada living with HIV/AIDS and there were 2,570 new HIV infections (range 1,940 to 3,200) in Canada in 2014.[3] Persons with HIV can be treated with antiretroviral (ARV) drugs, which help lower the level of HIV in the body, slow the spread of the virus in the body, and help the immune system respond to other infections.[2] Treatment can provide patients with a better opportunity to live a longer, healthier life and decrease their risk of transmitting the virus to others. Antiretroviral therapy (ART) has significantly reduced HIV-associated morbidity and mortality, as well as making HIV largely a manageable chronic condition.[4] If treatment is started early, there is increased probability of living a near-normal lifespan.[2] Patients consulted for this review indicated that stigma continues to be a major concern.

According to the US Department of Health and Human Services (DHHS) “Guidelines for the Use of Antiretroviral (ARV) Agents in Adults and Adolescents Living with HIV,” the ARV regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer (booster) (cobicistat or ritonavir).[4] The DHHS guidelines indicate that, once initiated, ART should be continued with the following key treatment goals: to maximally and durably suppress plasma HIV ribonucleic acid (RNA) (< 50 copies/mL); to restore and preserve immunologic function; to reduce HIV-associated morbidity and prolong the duration and quality of survival; and to prevent HIV transmission.[4] ART therapy is lifelong, and high levels of adherence are required. To support long-term adherence, several single-tablet regimens (STRs) are available.

Indication Under Review
As a complete regimen for the treatment of HIV-1 infection in adults with no known substitution associated with resistance to the individual components of B/FTC/TAF
Listing Criteria Requested by Sponsor
As per indication

The objective of this systematic review was to evaluate the efficacy and safety of the fixed-dose combination (FDC) bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF) 50 mg/200 mg/25 mg, once daily, as a treatment for HIV type 1 (HIV-1) infection in adults with no known substitution associated with resistance to the individual components of B/FTC/TAF. Of which, B is an integrase strand transfer inhibitor, and both emtricitabine (FTC) and tenofovir alafenamide (TAF) are nucleoside reverse transcriptase inhibitors.

Results and Interpretation

Included Studies

Five randomized controlled trials (RCTs) met the pre-specified inclusion criteria and were included to evaluate the comparative efficacy and safety of B/FTC/TAF. Two trials (Study 1489 and Study 1490) were randomized, double-blind, double-dummy, noninferiority trials undertaken in treatment-naive populations. In Study 1489 (N = 629), patients were randomized (1:1) to B/FTC/TAF (50 mg/200 mg/25 mg) once daily, or abacavir/dolutegravir/lamivudine (ABC/DTG/3TC, 600 mg/50 mg/300mg) once daily. In Study 1490 (N = 645), patients were randomized (1:1) to B/FTC/TAF (50 mg/200 mg/25 mg) once daily or DTG + FTC/TAF, (50 mg + 200 mg/25 mg), each once daily. Participants were enrolled from European Union countries, the US, and Canada. The majority of patients were white males aged 18 years or older with baseline HIV-1 RNA levels ≥ 500 copies/mL. Both trials are ongoing to 144 weeks, with the cut point for the manufacturer-provided data being when all randomized subjects had completed the week 48 visit or had prematurely discontinued study drugs before their week 48 visit. The primary end point was the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 (using the FDA-defined snapshot algorithm) with a noninferiority margin of –12%.

Three studies (Study 1844, Study 1878, and Study 1961) were undertaken in treatment-experienced/switch populations with virologic suppression of HIV-1 on their current regimen. All studies were noninferiority trials and randomized patients 1:1 to receive either B/FTC/TAF (50 mg/200 mg/25 mg) once daily or to stay on baseline regimen (SBR). The baseline regimens were different in each of the three studies. In studies 1844 and 1878, patients were enrolled from European Union countries, the US, and Canada. The majority of patients were white males aged 18 years or older with baseline HIV-1 RNA levels < 50 copies/mL. Study 1844 was a randomized (1:1), double-blind, double-dummy, noninferiority trial comparing B/FTC/TAF (50 mg/200 mg/25 mg) once daily with SBR of the FDC of ABC/DTG/3TC (600 mg/50 mg/300 mg) once daily. Study 1878 was an open-label noninferiority RCT with patients randomized (1:1) to B/FTC/TAF (50 mg/200 mg/25 mg) or SBR consisting of ritonavir (RTV)- or cobicistat (COBI or C)-boosted atazanavir (ATV) or darunavir (DRV) plus either FTC/tenofovir disoproxil fumarate (TDF) or ABC/3TC. Doses were not provided for the comparator. In Study 1961, women were enrolled from the US, Russia, Thailand, and Uganda. Patients were aged 18 years or older, with baseline HIV-1 RNA levels < 50 copies/mL. Study 1961 was an open-label, noninferiority RCT in which

patients were randomized (1:1) to B/FTC/TAF (50 mg/200 mg/25 mg) or to SBR of elvitegravir (E)/ C/FTC/TAF 150 mg/150 mg/200 mg/10 mg), E/C/FTC/TDF (150 mg/150 mg/200 mg/300 mg) or ATV + RTV + FTC/TDF (300 mg + 100 mg + 200 mg/300 mg). All trials are ongoing to 96 weeks, with the cut point for the manufacturer-provided data being when all randomized subjects had completed the week 48 visit or had prematurely discontinued study drugs before their week 48 visit. The primary outcome for all studies was the proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48 (using the FDA-defined snapshot algorithm), with a noninferiority margin of 4%.

According to the clinical expert consulted for this review, the comparators in all five trials may be appropriate treatment; however, he noted that the comparators in Study 1878 (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC) are older drugs that are not frequently used in Canadian practice. The trials are currently ongoing, and, given that the current data are limited to the 48-week time point, the durability of response will require evaluation when longer-term data are available.

Efficacy

In studies 1489 and 1490, 92% versus 93% and 89% versus 92% of patients receiving B/FTC/TAF versus ABC/DTG/3TC or DTG + FTC/TAF, respectively, achieved the primary end point of HIV-1 RNA < 50 copies/mL at 48 weeks. These results met with the pre-specified noninferiority margin of –12%. The between-treatment per cent differences at 48 weeks were –0.6% (95% confidence interval [CI], –4.8% to 3.6%) for Study 1489 and −3.5% (95% CI, −7.9% to 1.0%) for Study 1490, based on the analysis of the full analysis set (FAS). The results from the per-protocol (PP) analyses were consistent with those from the FAS analyses. Health-related quality of life (HRQoL) was measured in both studies using the Short Form (36) Health Survey (SF-36); however, data were not provided for Study 1490. In Study 1489, the median change in SF-36 mental component summary (MCS) from baseline to week 48 was 0.1 (interquartile range [IQR], –3.3 to 3.1) and 0.2 (IQR, –2.6 to 2.8) for B/FTC/TAF and ABC/DTG/3TC, respectively. The median change in SF-36 physical component summary (PCS) from baseline to week 48 was 2.3 (IQR, –1.6 to 9.0) and 2.1 (IQR, –4.0 to 7.0) for B/FTC/TAF and ABC/DTG/3TC, respectively. HRQoL was an exploratory outcome, and statistical analyses of these data were not planned to control for type I error. In Study 1489 and 1490, mean adherence was [redacted] and [redacted] for B/FTC/TAF versus ABC/DTG/3TC or DTG + FTC/TAF, respectively.

In Study 1844, 1.1% versus 0.4% of patients in the B/FTC/TAF versus ABC/DTG/3TC groups, respectively, had HIV-1 RNA ≥ 50 copies/mL at 48 weeks. These results met the pre-specified noninferiority margin of 4% (between-treatment per cent difference at 48 weeks: 0.7%; 95% CI, –1.0% to 2.8%). The results from the PP analysis were consistent with those from the FAS analysis. HRQoL was measured using the SF-36. The median change in the SF-36 PCS from baseline to week 48 was –0.4 (IQR, –3.6 to 2.7) and 0.2 (IQR, –2.3 to 2.7) for B/FTC/TAF and ABC/DTG/3TC, respectively. The median change in SF-36 MCS from baseline to week 48 was 0.3 (IQR, –3.0 to 4.6) and 0.1 (IQR, –3.9 to 3.5) for B/FTC/TAF and ABC/DTG/3TC, respectively. HRQoL was an exploratory outcome, and statistical analyses of these data were not planned to control for type I error. The mean adherence was [redacted] in the B/FTC/TAF and ABC/DTG/3TC groups, respectively.

In Study 1878, 1.7% versus 1.7% of patients in the B/FTC/TAF group versus SBR group, consisting of RTV- or COBI-boosted ATV or DRV + either FTC/TDF or ABC/3TC, respectively, had HIV-1 RNA ≥ 50 copies/mL at 48 weeks. These results met the pre-specified noninferiority margin of 4% (per cent difference at 48 weeks: 0.0%; 95% CI,

–2.5% to 2.5%). The results from the PP analysis were consistent with the FAS analysis. Virologic response data were not provided separately for the different baseline regimens. HRQoL data were not provided. The mean adherence was [redacted] in the B/FTC/TAF group and was not reported for the comparator.

In Study 1961, 1.7% versus 1.7% of patients in the B/FTC/TAF versus baseline regimens of E/C/FTC/TAF, E/C/FTC/TDF, or ATV + RTV + FTC/TDF, respectively, had HIV-1 RNA ≥ 50 copies/mL at 48 weeks. These results met the pre-specified noninferiority margin of 4% (per cent difference at 48 weeks: 0.0%; 95% CI, –2.9% to 2.9%). The results from the PP analysis were consistent with the FAS analysis. Virologic response data were not provided separately for the different baseline regimens. HRQoL was not measured. The mean adherence was [redacted].

Harms

In the treatment-naive trials, the majority of the study populations experienced at least one adverse event (AE) (82.5% to 89.8%). AEs were balanced across treatment groups. The most frequent AEs (> 10% of patients) were diarrhea, headache, and nausea. There were no deaths in Study 1489. There were three deaths in Study 1490 (B/FTC/TAF: one due to cardiac arrest following appendicitis and septic shock; DTG + FTC/TAF: one from unknown causes, one due to pulmonary embolism), none of which were deemed to be treatment-related by the manufacturer. A small proportion of patients withdrew from the trials due to AEs (in Study 1489: none from B/FTC/TAF, and 4 [1.3%] from ABC/DTG/3TC; in Study 1490: five [1.6%] from B/FTC/TAF and one (0.3%) from DTG + FTC/TAF). No patients developed treatment-emergent drug resistance. With respect to renal-related harms, in both trials, serum creatinine increased slightly, with similar magnitude in both treatment groups from baseline to week 48. However, week 48 serum creatinine was still within normal range. In both trials, estimated glomerular filtration rate (eGFR) decreased from baseline to week 48, slightly more so in the comparator arms containing DTG. The clinical expert indicated that this is a known AE of DTG. With respect to bone-related harms, neither trial revealed any clinically meaningful change in bone mineral density at the hip or spine.

In the treatment-experienced/switch trials, the majority of the study populations experienced at least one AE (65.8% to 80.3%). AEs were balanced across treatment groups. The most frequent AEs (> 10% of patients) were upper respiratory tract infection and nasopharyngitis. There were two deaths in Study 1844, both in the B/FTC/TAF group (one cardiac death as a result of hypertensive and atherosclerotic cardiovascular disease, one from unknown causes). There were two deaths in Study 1878 (B/FTC/TAF, one due to complications from lung cancer; SBR group, one due to blunt force trauma to the head). In Study 1961, there was one death (SBR group, one due to influenza). None of the deaths were deemed to be treatment-related by the manufacturer. A small proportion of patients withdrew from the study due to AEs (in Study 1844: six [2.1%] in the B/FTC/TAF group and two [0.7%] in the ABC/DTG/3TC group; in Study 1878: two [0.7%] in the B/FTC/TAF group and one [0.3%] in the SBR group; Study 1961: none in the B/FTC/TAF or SBR groups). No patients in Study 1844 developed treatment-emergent drug resistance. In Study 1878, one patient in the SBR group (on a regimen of RTV-boosted DRV + ABC/3TC) developed L74V in reverse transcriptase. In Study 1961, one patient in the SBR group (patient taking E/C/FTC/TAF) developed M184M/I/V. With respect to renal-related harms, in the three studies, renal function was not significantly compromised. Change in serum creatinine from baseline to 48 weeks in all three studies increased minimally and with similar magnitude in all treatment groups. Small and clinically insignificant changes in mean eGFR from baseline to week 48

were observed in treatment groups across the trials (Study 1844: B/FTC/TAF 1.8 mL/min, ABC/DTG/3TC –1.8 mL/min; Study 1878: B/FTC/TAF –3.4 mL/min, SBR 0.4 mL/min; Study 1961: B/FTC/TAF –2.1 mL/min, SBR –1.7 mL/min). With respect to bone-related harms, the three studies did not reveal any clinically meaningful change in bone mineral density at the hip or spine at 48 weeks.

Based on studies 1489 and 1490, the DHHS recently issued a statement regarding bictegravir, recommending B/FTC/TAF 50 mg/25 mg/200 mg once daily as one of the initial regimens for most people with HIV.[5]

Indirect Treatment Comparisons

[redacted] However, given a number of limitations, the network meta-analysis does not provide compelling evidence that the safety and efficacy of B/FTC/TAF [redacted]

Potential Place in Therapy[1]

The triple co-formulation B/FTC/TAF is the eighth STR to become available on the Canadian market (preceded by Atripla, Complera, Odefsey, Stribild, Genvoya, Triumeq, and Juluca).

Although treatment alternatives are welcome, there are no significant unmet needs for patients with a nonresistant virus in this era of HIV antiviral therapy. The available antivirals offer STR options for the majority of HIV-infected persons with nonresistant virus. They are convenient and increasingly free of immediate and long-term toxicity; drug interactions can occur but are manageable in most cases.

When patients adhere to therapy and take it as recommended (for instance, with food or without antacids), most of the available STRs suppress HIV replication in the vast majority of treated patients. The strength of B/FTC/TAF is in its simplicity of use. There are very few expected side effects (unlike Atripla), little renal or bone toxicity (unlike Atripla, Complera, and Stribild), no significant drug–drug interactions (unlike Genvoya or Stribild), no dietary restrictions (unlike Atripla, Complera, Odefsey, and Juluca), and no need for pre-testing for HLA B5701 (unlike Triumeq).

Because it avoids the concerns of other regimens, B/FTC/TAF may be prescribed immediately upon diagnosis with little concern for intolerance, inconvenience, or toxicity. It may be used as substitution for any of the previously mentioned options in cases of toxicity or inconvenience.

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

B/FTC/TAF would be a reasonable treatment option for almost any patient with a nonresistant virus. It can be taken at any time of day, with or without food, by patients with other comorbidities and on other medications. It may be very commonly prescribed as first-line therapy or as a switch medication (except in the case of virologic treatment failure) and may become the preferred therapy for most patients with nonresistant virus because of its ease of use.

Conclusions

In two RCTs conducted in treatment-naive patients with HIV-1, B/FTC/TAF was demonstrated to be noninferior to ABC/DTG/3TC and to DTG + FTC/TAF in achieving virologic suppression (HIV-1 RNA < 50 copies/mL) at week 48. In three RCTs conducted in virologically suppressed treatment-experienced patients with HIV-1, B/FTC/TAF was demonstrated to be noninferior to continuing treatment with (1) ABC/DTG/3TC, (2) RTV- or COBI-boosted ATV or DRV + either FTC/TDF or ABC/3TC, (3) E/C/FTC/TAF, (4) E/C/FTC/TDF, or (5) ATV + RTV + FTC/TDF, in terms of the proportion of patients experiencing virologic failure (HIV-1 RNA ≥ 50 copies/mL) at week 48. Harms were similar between treatment groups, and surrogates for renal and bone safety were unremarkable at week 48. Longer-term data are needed to the support the comparative efficacy and safety of B/FTC/TAF.

Table 1: Summary of Results: Treatment-Naive Population

Outcome	Study 1489		Study 1490	
	B/FTC/TAF (n = 314)	ABC/DTG/3TC (n = 315)	B/FTC/TAF (n = 320)	DTG + FTC/TAF (n = 325)
HIV-1 RNA < 50 copies/mL at week 48				
N (%)	290 (92.4)	293 (93.0)	286 (89.4)	302 (92.9)
Difference, % (95% CI)	–0.6 (–4.8 to 3.6)		–3.5 (–7.9 to 1.0)	
HIV-1 RNA ≥ 50 copies/mL at week 48				
N (%)	3 (1.0%)	8 (2.5%)	14 (4.4%)	4 (1.2%)
Difference, % (95% CI)	NR		NR	
Withdrawals				
Total, N (%)	18 (5.7)	14 (4.4)	24 (7.5)	18 (5.5)
SAEs				
n, N (%)	19 (6.1)	25 (7.9)	39 (12.2)	23 (7.1)
WDAEs				
n, N (%)	0	4 (1.3)	5 (1.6)	1 (0.3)
Notable harms				
Serum creatinine (mg/dL)				
N	314	315	320	325
Baseline mean, SD	0.92 (0.279)	0.92 (0.168)	0.93 (0.216)	0.89 (0.156)
Change from baseline at week 48 (SD)	0.09 (0.249)	0.11 (0.155)	0.12 (0.343)	0.12 (0.117)
eGFR (mL/min)				
N	314	315	320	325
Baseline mean, SD	131.0 (39.44)	128.8 (33.32)	122.8 (31.59)	129.2 (40.57)
Change from baseline at week 48 (SD)	[redacted]	[redacted]	[redacted]	[redacted]

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CI = confidence interval; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; FTC/TAF = emtricitabine/tenofovir alafenamide; NR = not reported; RNA = ribonucleic acid; SAE = severe adverse event, SD = standard deviation; WDAE= withdrawal due to adverse event.

Source: Clinical Study Report for Study1489,[6] Clinical Study Report for Study 1490.[7]

Table 2: Summary of Results: Treatment-Experienced/Switch Population

Outcome	Study 1844		Study 1878		Study 1961	
	B/FTC/TAF (n = 282)	ABC/DTG/3TC (n = 281)	B/FTC/TAF (n = 290)	SBR (n = 287)	B/FTC/TAF (n = 234)	SBR (n = 236)
HIV-1 RNA ≥ 50 copies/mL at week 48						
N (%)	3 (1.1)	1 (0.4)	5 (1.7)	5 (1.7)	4 (1.7)	4 (1.7)
Difference, % (95% CI)	0.7 (–1.0 to 2.8)		0.0 (–2.5 to 2.5)		0.0 (–2.9 to 2.9)	
HIV-1 RNA < 50 copies/mL at week 48						
N (%)	264 (93.6)	267 (95.0)	267 (92.1)	255 (88.9)	224 (95.7)	225 (95.3)
Difference, % (95% CI)	–1.4% (–5.5% to 2.6%)		3.2 (–1.6% to 8.2%)		0.4 (–3.7% to 4.5%)	
Withdrawals						
Total, N (%)	10 (3.5)	12 (4.3)	13 (4.5)	20 (7.0)	3 (1.3)	5 (2.1)
SAEs						
N (%)	15 (5.3)	22 (7.8)	17 (5.9)	20 (7.0)	7 (3.0)	8 (3.4)
WDAEs						
n, N (%)	6 (2.1)	2 (0.7)	2 (0.7)	1 (0.3)	0	0

Outcome	Study 1844		Study 1878		Study 1961	
	B/FTC/TAF (n = 282)	ABC/DTG/3TC (n = 281)	B/FTC/TAF (n = 290)	SBR (n = 287)	B/FTC/TAF (n = 234)	SBR (n = 236)
Notable harms						
Serum creatinine (mg/dL)						
N	282	281	290	287	234	236
Baseline mean, SD	1.06 (0.196)	1.06 (0.179)	0.98 (0.213)	0.98 (0.183)	[redacted]	[redacted]
Change from baseline at week 48 (SD)	0.00 (0.125)	0.02 (0.121)	0.05 (0.121)	0.00 (0.119)	[redacted]	[redacted]
eGFR (mL/min)						
N	282	281	290	287	234	236
Baseline mean, SD	104.3 (32.16)	104.9 (30.78)	109.9 (30.97)	108.4 (31.75)	[redacted]	[redacted]
Change from baseline at week 48 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ABC/DTG/3TC = abacavir/dolutegravir /lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CI = confidence interval; eGFR = estimated glomerular filtration rate; RNA = ribonucleic acid; SAE = severe adverse event; SBR = stay on baseline regimen; SD = standard deviation; WDAE = withdrawal due to adverse event.

Source: Clinical Study Report Study 1844,[8] Clinical Study Report Study 1878,[9] Clinical Study Report Study 1961.[10]

Introduction

Disease Prevalence and Incidence

Human immunodeficiency virus is the virus responsible for causing HIV infection.[1] HIV is transmitted by infected body fluids such as blood, semen, fluid from the rectum, fluid from the vagina, and breast milk.[2] The risks associated with becoming infected with HIV are predominantly behaviour-based and largely attributed to having unprotected sex with an infected person or sharing drug paraphernalia (e.g., needles, syringes, cookers, spoons) with an infected person.[2] HIV gradually destroys the immune system by destroying CD4 cells. CD4 are white blood cells that are critically important in helping the body fight infection. HIV infection compromises the immune system's ability to mount an effective immunological response to opportunistic pathogens and certain cancers.[11] Left untreated, HIV infection can progress to AIDS and, ultimately, death. Persons with HIV can be treated with antiretroviral (ARV) drugs, which help lower the level of HIV in the body, slow the spread of the virus in the body, and help the immune system respond to other infections.[2] Antiretroviral therapy (ART) has improved steadily since the introduction of potent combination therapy in 1996.[4] Treatment can provide patients with a better opportunity to live a longer, healthier life and decrease their risk of transmitting the virus to others. ART has significantly reduced HIV-associated morbidity and mortality, making HIV largely a manageable chronic condition.[4] If treatment is started early, there is increased probability of living a near-normal lifespan.[2] Patients consulted for this review indicated that stigma is a major concern.

Based on surveillance data, the Public Health Agency of Canada estimates that, at the end of 2014, there were approximately 75,500 people in Canada living with HIV/AIDS.[3] Among persons living with HIV/AIDS, approximately 22% are women and 78% are men.[3] The Public Health Agency of Canada estimates there were 2,570 new HIV infections (range 1,940 and 3,200) in Canada in 2014.[3] The estimated incidence rate in Canada in 2014 was 7.2 per 100,000 population (range between 5.5 and 9.0 per 100,000).[3] Approximately one in five people with HIV remain undiagnosed.[2] Among those diagnosed with HIV in 2014, 31.6% of new infections were diagnosed among people aged 30 to 39 years, and 22.8% in the 40- to 49-year age group.[3] Among cases in which exposure category was known, 48.8% were attributed to men who have sex with men, 29.2% to heterosexual contact, and 13.1% to injection drug use.[3]

Standards of Therapy

According to the US Department of Health and Human Services (DHHS) "Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV," the ARV regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic enhancer (booster) (cobicistat or ritonavir).[4] The clinical expert consulted for this review indicated that the DHHS guidelines are used in Canada.

The DHHS guidelines indicate that, once initiated, ART should be continued with the following key treatment goals: maximally and durably suppress plasma HIV ribonucleic acid (RNA) (< 50 copies/mL); restore and preserve immunologic function; reduce HIV-

associated morbidity and prolong the duration and quality of survival; and prevent HIV transmission.[4] ARV therapy is lifelong, and high levels of adherence are required. To support long-term adherence, several single-tablet regimens (STRs) are available.

According to the clinical expert consulted for this review, there is currently no unmet therapeutic need for patients with a nonresistant virus.

Drug

Bictegravir (B) 50 mg/emtricitabine (F) 200 mg/tenofovir alafenamide (TAF) 25 mg is an oral STR indicated as a complete regimen for the treatment of HIV type 1 (HIV-1) infection in adults with no known substitution associated with resistance to the individual components of B/FTC/TAF. The reimbursement request from the manufacturer is in accordance with the indication.

Biktarvy consists of an INSTI and two NRTIs. B, an INSTI, "binds to the integrase active site and blocks the strand transfer step of retroviral DNA integration, which is essential for the HIV replication cycle."[12] Emtricitabine (FTC), an NRTI, "inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination."[12] Tenofovir alafenamide (TAF), an NRTI, "inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination."[12]

Key characteristics of STRs and other commonly recommended ARV regimens are presented in Table 3.

Table 3: Key Characteristics of STRs and Other Commonly Recommended Antiretroviral Therapy Regimens

Comparator Regimens	Brand	Dosage Strengths[a]	Indications[b]	Key Side Effects/Safety Issues
Single-Tablet Regimens				
DTG/ABC/3TC	Triumeq	**DTG**: 50 mg **ABC**: 600 mg **3TC**: 300 mg	Treatment of HIV-1 infection in adults and adolescents aged ≥ 12 years and weighing ≥ 40 kg[13]	**DTG**: insomnia, headache, depression; early benign increase in SCr[14,15] **ABC**: risk of severe hypersensitivity reaction in genetically susceptible patients; possible increased risk for MI[14,15] **3TC**: generally well tolerated[14]
EVG/c/TAF/FTC	Genvoya[c]	**EVG**: 150 mg **c**: 150 mg **FTC**: 200 mg **TAF**: 10 mg	A complete regimen for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg) and with no known RAMs to the individual components of Genvoya[16]	**EVG:** nausea, diarrhea, insomnia, headache, depression; early benign increase in SCr[1,14,15] **c**: can falsely increase SCr[15] **FTC**: discoloration of skin (hands/feet)[15] **TAF:** Similar to TDF, but may have less renal and bone toxicity[17]
RPV/TAF/FTC	Odefsey[c]	**RPV**: 25 mg **TAF**: 25 mg **FTC**: 200 mg	A complete regimen for the treatment of adults infected with HIV-1 with no known RAMs to the NNRTI class, tenofovir, or FTC, and with a VL ≤ 100,000 copies/mL[18]	**RPV**: depression, insomnia, rash, headache; early benign increase in SCr[14] **TAF:** Similar to TDF, but may have less renal and bone toxicity[17] **FTC**: discoloration of skin (hands/feet)[15]

Comparator Regimens	Brand	Dosage Strengths[a]	Indications[b]	Key Side Effects/Safety Issues
DTG/RPV	Juluca	**DTG:** 50 mg **RPV:** 25 mg	A complete regimen to replace the current antiretroviral regimen for the treatment of HIV-1 infection in adults with virologically stable and suppressed HIV-1 (RNA < 50 copies/mL)[19]	**DTG**: insomnia, headache, depression; early benign increase in SCr[14,15] **RPV**: depression, insomnia, rash, headache; early benign increase in SCr[14]
DRV/c/TDF/FTC	Symtuza	**DRV:** 800 mg **c**: 150 mg **TAF**: 10 mg **FTC**: 200 mg	Indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight ≥ 40 kg) and with no known mutations associated with resistance to the individual components of Symtuza[20]	**DRV:** diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[14,15] **c**: can falsely increase SCr[15] **TAF: s**imilar to TDF, but may have less renal and bone toxicity[17] **FTC**: discoloration of skin (hands/feet)[15]
EVG/c/TDF/FTC	Stribild[c]	**EVG**: 150 mg **c**: 150 mg **FTC**: 200 mg **TDF**: 300 mg	A complete regimen for the treatment of adults aged ≥ 18 years infected with HIV-1 with no known mutations to the INSTI class, tenofovir, or FTC[21]	**EVG:** nausea, diarrhea, insomnia, headache, depression; early benign increase in SCr[1,14,15] **c**: can falsely increase SCr[15] **FTC**: discoloration of skin (hands/feet)[15] **TDF**: renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[14]
RPV/TDF/FTC	Complera[c]	**RPV**: 25 mg **TDF**: 300 mg **FTC**: 200 mg	A complete regimen for the treatment of adults infected with HIV-1 with no known RAMs to the NNRTI class, tenofovir, or FTC, and with a VL ≤ 100,000 copies/mL[22]	**RPV**: depression, insomnia, rash, headache; early benign increase in SCr[14] **TDF**: renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[14] **FTC**: discoloration of skin (hands/feet)[15]
EFV/TDF/FTC	Atripla[d]	**EFV**: 600 mg **TDF**: 300 mg **FTC**: 200 mg	For use alone as a complete regimen or in combination with other ARV drugs for the treatment of HIV-1 infection in adults[23]	**EFV**: insomnia, vivid dreams, depressed mood, dizziness, headache, rash; avoid in patients with history of anxiety, depression, or psychosis; contraindicated in first trimester of pregnancy[14,15] **TDF**: renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[14] **FTC**: discoloration of skin (hands/feet)[15]
Additional Relevant Comparator Regimens				
DRV/c + TAF/FTC	Prezcobix[c] Descovy	**DRV/c**: 800 mg/150 mg **TAF/FTC**: 10 mg/200 mg 25 mg/200 mg	In combination with other ARV drugs for the treatment of HIV-1 infection in treatment-naive and in treatment-experienced patients without DRV RAMs[24] In combination with other ARVs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg)[25]	**DRV**: diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[14,15] **c**: can falsely increase SCr[15] **TAF**: similar to TDF, but may have less renal and bone toxicity[17] **FTC**: discoloration of skin (hands/feet)[15]

Comparator Regimens	Brand	Dosage Strengths[a]	Indications[b]	Key Side Effects/Safety Issues
DTG + TAF/FTC	Tivicay Descovy	**DTG**: 50 mg **TAF/FTC:** 10 mg/200 mg 25 mg/200 mg	Treatment of HIV-1 infection in adults and in INSTI-naive children weighing ≥ 30 kg[26] In combination with other ARVs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg)[25]	**DTG**: insomnia, headache, depression; early benign increase in SCr[14,15] **TAF:** similar to TDF, but may have less renal and bone toxicity[17] **FTC**: discoloration of skin (hands/feet)[15]
DRV + r + TDF/FTC	Prezista[c]	**DRV**: 800 mg	Co-administered with 100 mg ritonavir and with other ARV drugs for the treatment of HIV-1 infection[27]	**DRV**: diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[14,15] **r**: diarrhea, nausea, headache, paresthesia, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[14,15] **TDF**: renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[15] **FTC**: discoloration of skin (hands/feet)[15]
	Norvir[c]	**r:** 100 mg	In combination with other ARV drugs for the treatment of HIV infection when therapy is warranted[28]	
	Truvada, generics	**TDF**: 300 mg **FTC**: 200 mg	In combination with other ARV drugs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults[29]	
DTG + TDF/FTC	Tivicay	**DTG**: 50 mg	Treatment of HIV-1 infection in adults and in INSTI-naive children weighing ≥ 30 kg[26]	**DTG**: insomnia, headache, depression; early benign increase in SCr[14,15] **TDF**: renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[14] **FTC**: discoloration of skin (hands/feet)[15]
	Truvada, generics	**TDF**: 300 mg **FTC**: 200 mg	In combination with other ARV drugs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults[29]	

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMD = bone mineral density; c = cobicistat; DRV = darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HIV-1 = HIV type 1; INSTI = integrase strand transfer inhibitor; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; r = low-dose ritonavir; RAM = resistance-associated mutation; RPV = rilpivirine; SCr = serum creatinine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; VL = viral load.

[a] All regimens are administered orally once daily.[1]

[b] Health Canada indication.

[c] Must be taken with food or a meal.[1]

[d] Must be taken on an empty stomach.[1]

Source: Prezcobix product monograph,[24] Tivicay product monograph,[26] Descovy product monograph,[25] Genvoya product monograph,[16] Odefsey product monograph,[18] Triumeq product monograph,[13] Truvada product monograph,[29] Prezista product monograph,[27] Norvir product monograph,[28] Stribild product monograph,[21] Complera product monograph,[22] Atripla product monograph,[23] Juluca product monograph,[19] Symtuza product monograph,[20] e-CPS,[14] RxFiles,[15] AIDSinfo.[1]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of B/FTC/TAF 50 mg/200 mg/25 mg (Biktarvy) for the treatment of HIV-1 in adults with no known substitution associated with resistance to the individual components of B/FTC/TAF.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CADTH Common Drug Review (CDR) and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adults with HIV-1 infection with no known substitution associated with resistance to the individual's components of B/FTC/TAF Subgroups: • Baseline VL (treatment-naive; < 100,000 copies/mL or ≥ 100,000 copies/mL) • Treatment-naive versus treatment-experienced Baseline regimens (treatment-experienced /switch)
Intervention	Bictegravir 50 mg / emtricitabine 200 mg / tenofovir alafenamide 25 mg in fixed-dose co-formulation taken orally once daily or co-administered individually at the Health Canada–recommended dosages
Comparators	Standard care triple ARV regimen: either 2 NRTIs + 1 INSTI; 2 NRTIs + 1 NNRTI; or 2 NRTIs + 1 PI (boosted with ritonavir or cobicistat) or other recommended treatments
Outcomes	**Key efficacy outcomes:** • Proportion of patients with VL < 50 copies / mL (FDA-defined snapshot algorithm) • Proportion of patients with VL ≥ 50 copies / mL (FDA-defined snapshot algorithm) **Other efficacy outcomes:** • Resistance • Quality of life • Adherence **Harms outcomes:** • SAEs • AEs • WDAEs Notable harms (renal, bone, anxiety, depression, insomnia, headache, diarrhea, nausea, vomiting)
Study Design	Published and unpublished phase III and IV RCTs

ARV = antiretroviral; AE = adverse event; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; HIV-1 = HIV type 1; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RCT = randomized controlled trial; SAE = serious adverse event; VL = viral load; WDAE = withdrawal due to adverse event.

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 ALL (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via 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 bictegravir, emtricitabine, tenofovir, and Biktarvy.

No filters were applied to limit the retrieval by study type. 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 May 30, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on September 19, 2018. 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 *Grey Matters* checklist (https://www.cadth.ca/grey-matters): regulatory approvals, health technology assessments, clinical practice guidelines, health economics, and advisories and warnings. 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 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 5 and Table 6; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of five studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5 and Table 6. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

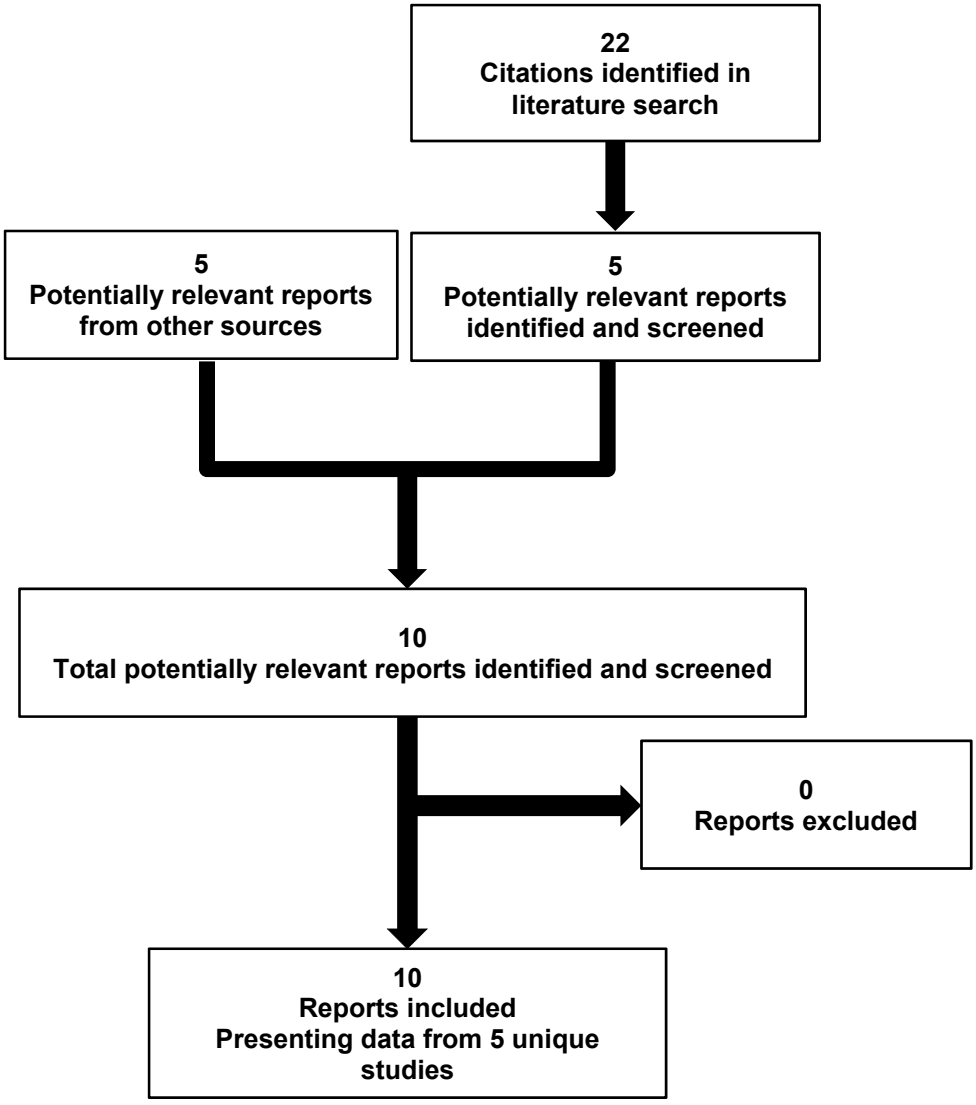


Table 5: Details of Included Studies: Treatment-Naive

		Study 1489	Study 1490
Designs and Populations	**Study Design**	Phase III DB RCT (noninferiority)	Phase III DB RCT (noninferiority)
	Locations	122 centres in 9 countries: Belgium, Canada, Dominican Republic, France, Germany, Italy, Spain, UK, and the US	126 centres in 10 countries: Australia, Belgium, Canada, Dominican Republic, France, Germany, Italy, Spain, UK, and the US
	Randomized (N)	631	657
	Inclusion Criteria	• Age ≥ 18 years • ART-naive • HLA-B*5701-negative • Plasma HIV-1 RNA ≥ 500 copies/mL • Genotype demonstrating sensitivity to FTC, tenofovir, 3TC, and ABC • eGFR ≥ 50 mL/min • Absence of chronic hepatitis B virus (HBV) infection	• Age ≥ 18 years • ART-naive • Plasma HIV-1 RNA levels ≥ 500 copies/mL at screening • Screening genotype report showed sensitivity to FTC and tenofovir (TFV) • eGFR ≥ 30 mL/min
	Exclusion Criteria	• Opportunistic illness indicative of Stage 3 HIV diagnosed with 30 days before screening • Acute hepatitis in the 30 days before study entry • Active tuberculosis	• Opportunistic illness indicative of Stage 3 HIV diagnosed within the 30 days before screening • Acute hepatitis in the 30 days before study entry • Active tuberculosis
Drugs	**Intervention**	B/FTC/TAF (50 mg/200 mg/25 mg) FDC tablet once daily, without regard to food	B/FTC/TAF 50 mg/200 mg/25 mg FDC tablet once daily, without regard to food
	Comparator(s)	ABC/DTG/3TC (600 mg/50 mg/300 mg) FDC tablet administered orally, once daily, without regard to food	DTG (50 mg) + FTC/TAF (200 mg/25 mg) FDC administered orally, once daily, without regard to food
Duration	**Phase**		
	Run-in	NA	NA
	Double-blind	144 weeks	144 weeks
	Follow-up	48 weeks (open-label)	48 weeks
Outcomes	**Primary End Point**	Proportion of subjects who achieved HIV-1 RNA < 50 copies/mL at week 48, as determined by the US FDA-defined snapshot algorithm	Proportion of subjects who achieved HIV-1 RNA < 50 copies/mL at week 48, as determined by the US FDA-defined snapshot algorithm
	Other End Points	**Other efficacy end points** • Proportion of patients who achieved HIV-1 RNA < 20 copies/mL at week 48 • Change from baseline in log10 HIV-1 RNA • Change from baseline in CD4 cell count at week 48 **Other Outcomes** • PROs (Short Form [36] Health Survey [SF-36]; HIV Symptoms Distress Module; Work Productivity and Activity Impairment Questionnaire [WPAI]; and Pittsburgh Sleep Quality Index [PSQI] questionnaire)	**Other efficacy end points** • Proportion of patients who achieved HIV-1 RNA < 20 copies/mL at week 48 • Change from baseline in log10 HIV-1 RNA • Change from baseline in CD4 cell count at week 48 **Other Outcomes** • PROs (Short Form [36] Health Survey [SF-36]; HIV Symptoms Distress Module; Work Productivity and Activity Impairment Questionnaire [WPAI]; and Pittsburgh Sleep Quality Index [PSQI] questionnaire)
Notes	**Publications**	Gallant et al.[30] Wohl et al.[31]	Sax et al.[32]

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; ART = antiretroviral therapy; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DB = double-blind; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; FTC/TAF = emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; FTC = emtricitabine; HIV-1 = HIV type 1; NA = not applicable; PRO = patient-reported outcome; RCT = randomized controlled trial; RNA = ribonucleic acid.

Source: Source: Clinical Study Report Study1489,[6] Clinical Study Report Study 1490.[7]

Table 6: Details of Included Studies: Treatment-Experienced/Switch

		Study 1844	Study 1878	Study 1961
Designs and Populations	**Study Design**	DB, active-control phase III RCT (noninferiority)	OL, active-control phase III RCT (noninferiority)	OL, active-controlled phase III RCT (noninferiority)
	Locations	96 study centres in 9 countries: Australia, Belgium, Canada, France, Germany, Italy, Spain, UK, and US (including Puerto Rico)	121 study centres in 10 countries: US, UK, Germany, Australia, Canada, France, Spain, Belgium, Italy, Dominican Republic	58 study centres in 5 countries: US (including Puerto Rico), Russia, Thailand, Dominican Republic, Uganda
	Randomized (N)	567	578	472
	Inclusion Criteria	• Age ≥ 18 years • Currently receiving an ARV regimen of DTG + ABC/3TC, or ABC/DTG/3TC FDC for ≥ 3 months before the screening visit • HIV-1 RNA < 50 copies/mL at the screening visit • Adequate renal function: eGFR ≥ 50 mL/min (≥ 0.83 mL/sec) according to the Cockcroft–Gault formula • Serum amylase ≤ 5 × ULN; Life expectancy ≥ 1 year • No documented or suspected resistance to FTC, tenofovir (TFV), DTG, ABC, or 3TC including, but not limited, to the reverse transcriptase resistance mutations K65R and M184V/I	• Age ≥ 18 years • Currently receiving a stable once daily ARV regimen consisting of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months preceding the screening visit • HIV-1 RNA < 50 copies/mL at the screening visit • Adequate renal function: eGFR ≥ 50 mL/min (≥ 0.83 mL/sec) according to the Cockcroft–Gault formula • No documented or suspected resistance to FTC, tenofovir (TFV), ABC or 3TC, including but not limited to the reverse transcriptase resistance mutations K65R and M184V/I • No previous use of any approved or experimental INSTI	• Female (at birth), age ≥ 18 years • Currently on a stable ARV regimen of E/C/FTC/TAF, E/C/FTC/TDF, or ATV + RTV + FTC/TDF continuously for ≥ 12 consecutive weeks preceding the screening visit • Completion of the week 48 OLE visit or any post-week 48 OLE visits in Study GS-US-236-0128, completion of the week 96 visit or any post-week 96 visits in Study GS-US-292-0109, or completion of the week 144 visit or any post-week 144 visits in studies GS-US-292-0104 or GS-US-292-0111 • Documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 12 weeks preceding the screening visit. After reaching HIV-1 RNA < 50 copies/mL, single values of HIV-1 RNA ≥ 50 copies/mL followed by resuppression to < 50 copies/mL were allowed • HIV-1 RNA < 50 copies/mL at screening • Adequate renal function: eGFR ≥ 50 mL/min (≥ 0.83 mL/sec) according to the Cockcroft–Gault formula • No documented or suspected resistance to FTC, TFV, ATV, or elvitegravir including, but not limited to, the reverse transcriptase resistance mutations K65R and M184V/I
	Exclusion Criteria	• An opportunistic illness indicative of Stage 3 HIV diagnosed within the 30 days before screening • Active, serious	• An opportunistic illness indicative of Stage 3 HIV diagnosed within the 30 days before screening • Active, serious infections (other than HIV-1 infection)	• An opportunistic illness indicative of Stage 3 HIV diagnosed within the 30 days before screening • Active, serious infections (other than HIV-1 infection)

		Study 1844	Study 1878	Study 1961
		infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days before day 1 • Acute hepatitis in the 30 days before study entry • Chronic hepatitis B virus (HBV) infection • Active tuberculosis infection	requiring parenteral antibiotic or antifungal therapy within 30 days before day 1 • Acute hepatitis in the 30 days before study entry • Chronic HBV infection in subjects not on a TDF-containing regimen • Active tuberculosis infection	requiring parenteral antibiotic or antifungal therapy within 30 days before day 1 • Acute hepatitis in the 30 days before study entry • Active tuberculosis infection
Drugs	**Intervention**	B/FTC/TAF (50 mg/200 mg/25 mg) FDC tablet once daily, without regard to food	B/FTC/TAF (50 mg/200 mg/25 mg) FDC tablet once daily, without regard to food	B/FTC/TAF (50 mg/200 mg/25 mg) FDC tablet once daily, without regard to food
	Comparator(s)	ABC/DTG/3TC (600 mg/50 mg/300 mg) FDC tablet administered orally, once daily, without regard to food	Current ARV regimen consisting of: Boosted ATV + ABC/3TC Boosted DRV + ABC/3TC Boosted ATV + FTC/TDF Boosted DRV + FTC/TDF *boosted with either RTV or COBI administered orally once daily with food	Remained on current ARV regimen consisting of: • E/C/FTC/TAF (150 mg/150 mg/200 mg/10 mg), • E/C/FTC/TDF (150 mg/150 mg/200 mg/300 mg), or • ATV (300 mg) + RTV (100 mg) + FTC/TDF (200 mg/300 mg) administered orally once daily with food
Duration	**Phase**			
	Run-in	NA	NA	NA
	Double-blind	48 weeks (at least)	48 weeks (at least)	48 weeks (at least)
	Follow-up	OL extension of up to 96 weeks	OL extension of up to 96 weeks (maximum 144 weeks)	OL extension of up to 96 weeks
Outcomes	**Primary End Point**	Proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48, as determined by the US FDA-defined snapshot algorithm	Proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48, as determined by the US FDA-defined snapshot algorithm	Proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48, as determined by the US FDA-defined snapshot algorithm
	Other End Points	**Secondary Outcomes** • Proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 • Proportion of patients with HIV-1 RNA < 20 copies/mL at week 48 • Change from baseline in CD4 cell count at week 48 **Other Outcomes** • PROs (Short Form [36] Health Survey [SF-36]; HIV Symptoms Distress Module; Work	**Other Efficacy Outcomes** • Proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 • Proportion of patients with HIV-1 RNA < 20 copies/mL at week 48 • Change from baseline in CD4 cell count at week 48 **Other Outcomes** • PROs (Short Form [36] Health Survey [SF-36]; HIV Symptoms Distress Module; Work Productivity and Activity Impairment Questionnaire	**Other Efficacy Outcomes** • Proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 • Proportion of patients with HIV-1 RNA < 20 copies/mL at week 48 • Change from baseline in CD4 cell count at week 48 **Safety** • AEs, SAEs, markers of renal function

		Study 1844	Study 1878	Study 1961
		Productivity and Activity Impairment Questionnaire [WPAI]; and Pittsburgh Sleep Quality Index [PSQI] questionnaire) **Safety** • AEs, SAEs, markers of renal function, bone mineral density (hip and spine)	[WPAI]) **Safety** • AEs, SAEs, markers of renal function	
Notes	**Publications**	Molina et al.[33] Wohl et al.[31]	Daar et al.[34]	None

ABC/3TC = abacavir/lamivudine; AE = adverse event; ARV = antiretroviral; ATV = atazanavir; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; COBI = cobicistat; DB = double-blind; DTG = dolutegravir; DRV = darunavir; E/C/FTC/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; E/C/FTC/TDF = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; eGFR = estimated glomerular filtration rate; FDC = fixed-dose combination; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = HIV type 1; NA = not applicable; OL = open-label; OLE = open-label extension; PRO = patient-reported outcome; RCT = randomized controlled trial; RNA = ribonucleic acid; RTV = ritonavir; SAE = serious adverse event; TFV= tenofovir; ULN = upper limit of normal.

Source: Clinical Study Report Study 1844,[8] Clinical Study Report Study 1878,[9] Clinical Study Report Study 1961.[10]

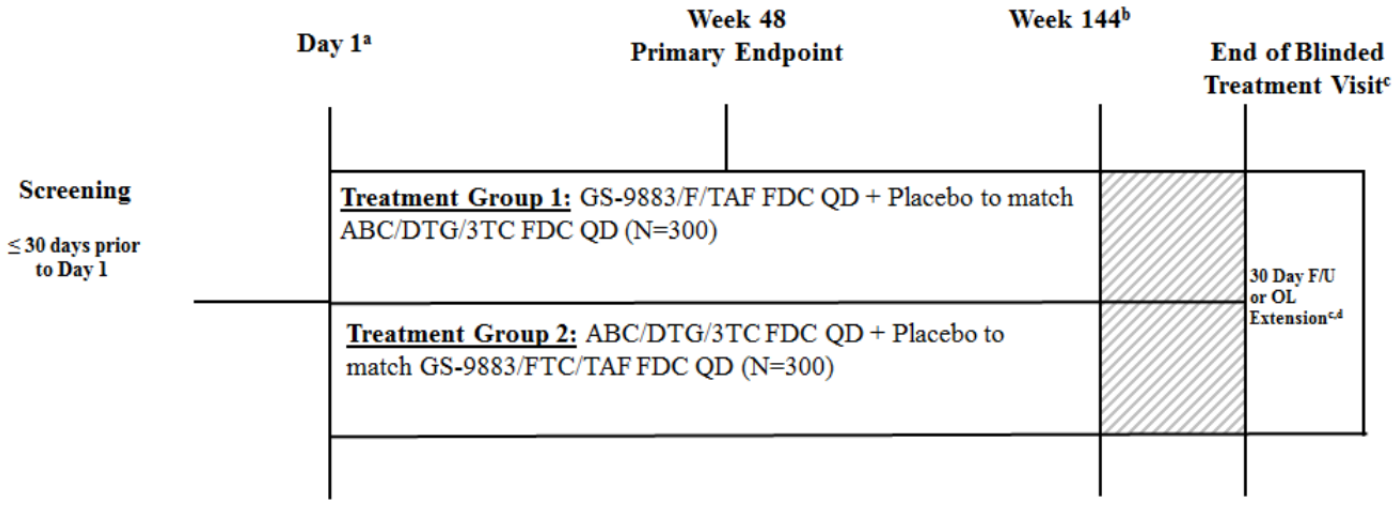
Included Studies

Description of Studies

Treatment-Naive

Study 1489 (N = 631; nine countries) and Study 1490 (N = 657; 10 countries) are phase III, randomized (1:1), multi-centre, double-blind, parallel-group, noninferiority trials. Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 to ≤ 400,000 copies/mL, or > 400,000 copies/mL), CD4 cell count (< 50 cells/μL, 50 to 199 cells/μL, or ≥ 200 cells/μL), and region (US or outside the US). Both studies enrolled treatment-naive patients. Study 1489 randomized patients to receive either B/FTC/TAF or abacavir/dolutegravir/lamivudine (ABC/DTG/3TC). Study 1490 randomized patients to receive either B/FTC/TAF or dolutegravir/emtricitabine/tenofovir alafenamide (DTG/FTC/TAF). The primary objective of both trials was to test the noninferiority of B/FTC/TAF versus the comparator. The primary end point was the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 (the FDA-defined snapshot algorithm). Both trials are ongoing to 144 weeks, with the cut point for the manufacturer-provided data being when all randomized subjects had completed the week 48 visit or had prematurely discontinued study drugs before their week 48 visit. The design of Study 1489 is displayed in Figure 2 (Study 1490 is identical).

Figure 2: Design of Study 1489[6]



ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; FDC = fixed-dose combination; F/U = follow-up; GS-9883/F (or FTC)/TAF = bictegravir/emtricitabine/tenofovir alafenamide; OL = open-label; QD = once daily.

[a] Following the day 1 visit, subjects returned for study visits at weeks 4, 8, 12, and then every 12 weeks through week 144.

[b] After week 144, all subjects continue to take their blinded study drugs and attend visits every 12 weeks until the end-of-blinded-treatment visit.

[c] Once the last subject completes the week 144 visit and the manufacturer completes the week 144 analysis, all subjects return to the clinic (preferably within 30 days) for an end-of-blinded-treatment visit. At that visit, if the safety and efficacy of B/FTC/TAF is demonstrated following review of unblinded data, subjects in a country where B/FTC/TAF is not available are given the option to receive B/FTC/TAF in an open-label extension for up to 48 weeks, or until the product becomes accessible to subjects through an access program, or until the manufacturer elects to discontinue the study in that country, whichever occurs first.

[d] Subjects who complete the study through the end-of-blinded-treatment visit and do not continue in the open-label B/FTC/TAF extension phase return to the clinic after the end-of-blinded-treatment visit for a 30-day follow-up visit.

Treatment-Experienced/Switch

Study 1844 (N = 567, nine countries; men and women; stratified by prior treatment regimen), Study 1878 (N = 578; 10 countries; men and women; randomization stratified by the prior treatment-regimen group), and Study 1961 (n = 472; five countries; women only; randomization stratified by prior treatment regimen; women with virologically suppressed HIV-1 who had participated in previous studies by the manufacturer may have been eligible to enrol) are phase III, randomized multi-centre, noninferiority trials. Study 1844 is double blind, and Study 1878 and 1961 are open label. The primary end point was the proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48 (the FDA snapshot algorithm). All trials are ongoing to 96 weeks, with the cut point for the manufacturer-provided data being when all randomized subjects had completed the week 48 visit or had prematurely discontinued study drugs before their week 48 visit.

Populations

Inclusion and Exclusion Criteria

Treatment-Naive

Study 1489 and Study 1490 enrolled ART-naive patients aged ≥ 18 years of age with baseline HIV-1 RNA levels ≥ 500 copies/mL and adequate renal function. In Study 1489, patients had to demonstrate sensitivity (via genotyping) to FTC, tenofovir (TFV), 3TC, and

ABC. In Study 1490, patients had to demonstrate sensitivity (via genotyping) to FTC and TFV. In Study 1489, patients with chronic hepatitis B virus infection were excluded. In both studies, patients with an opportunistic illness indicative of Stage 3 HIV diagnosed within 30 days before screening, alcohol or substance use judged to potentially interfere with study compliance, and pregnant and/or breastfeeding women were excluded. In Study 1489, patients were excluded if they were receiving ongoing therapy with any of the following medications, including drugs not to be used with FTC, TAF, B, DTG, ABC and 3TC: dofetilide, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, rifampin, rifapentine, any ARV drug that is not part of the study regimen, cisapride, St. John's Wort, or echinacea. In Study 1490, patients were excluded if they were receiving any of the medications listed for Study 1489, including drugs not to be used with FTC, TAF, B, and DTG (Table 5).

Treatment-Experienced/Switch

Studies 1844, 1878, and 1961 (women only) enrolled patients aged ≥ 18 years, currently receiving an ARV regimen (Study 1844, three months or more; Study 1878, six months or more; Study 1961, 12 weeks or more), with virologically suppressed HIV-1 (RNA < 50 copies/mL at baseline), with adequate renal function. Patients were excluded from these studies if they had an opportunistic illness indicative of Stage 3 HIV diagnosed within the 30 days before screening, pregnant and/or breastfeeding women, alcohol or substance use judged to potentially interfere with study compliance, and acute hepatitis within 30 days before study entry. In Study 1844 and Study 1878, patients were excluded if they had a chronic hepatitis B virus infection (Table 6).

In Study 1844, patients were excluded if they were receiving ongoing therapy with any of the following medications: dofetilide, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, rifampin, rifapentine; any antiretroviral drug that is not part of the study regimen; cisapride, St. John's Wort, or echinacea, including drugs not to be used with FTC, TAF, B, DTG, ABC, or 3TC.

In studies 1878 and 1961, patients were excluded if they were receiving ongoing therapy with any of the medications as for Study 1844 as well as alfuzosin, amiodarone, dronedarone, lurasidone, pimozide, irinotecan, ergotamine, ergonovine, dihydroergotamine, methylergonovine, ergometrine, simvastatin, lovastatin, sildenafil, midazolam, triazolam, bepridil, ranolazine, or any ARV drug that was not part of the study regimen.

Baseline Characteristics

Treatment-Naive

Baseline characteristics in both Study 1489 and Study 1490 were well balanced between treatment groups. Study 1489 enrolled a slightly younger population (mean age 34 years) compared with Study 1490 (mean age 37 years). The majority of patients in both studies were male (90%). Patients enrolled in both studies were mostly white (> 55%). The proportion of black patients enrolled was slightly greater in Study 1489 (35%) compared with Study 1490 (30%). In both studies, > 80% of patients had HIV-1 RNA ≤ 100,000 copies/mL. The majority of patients both studies were asymptomatic (91% in Study 1489 and 89% in Study 1490). However, a greater proportion of patients in Study 1490 were diagnosed with AIDS (7.5% to 8.0%) compared with Study 1489 (3.8% to 4.8%). In a response to a Request for Information, the manufacturer clarified that "Participants who had AIDS by the way of having CD4 count below 200 cells/mm^3 were eligible for the study, as long as they did not have an acute opportunistic illness indicative of Stage 3 HIV within 30 days of screening. If participants had an AIDS-defining opportunistic illness indicative of Stage 3 HIV within the 30 days of screening, they were excluded from the study regardless of their CD4 count."[35] A small proportion (< 2%) of patients in both trials were co-infected with hepatitis C (Table 87).

Treatment-Experienced/Switch

Overall, patients enrolled in the treatment-experienced/switch trials were older, had worse renal function (according to estimated glomerular filtration rate [eGFR]), and were more likely to have AIDS compared with the patients enrolled in the treatment-naive trials. Baseline characteristics in Study 1844, Study 1878, and Study 1961 were well balanced between treatment groups. The majority of patients enrolled in Study 1844 and Study 1878 were male (> 87% and > 81%, respectively). Only women were enrolled in Study 1961. The majority of patients enrolled in Study 1844 and 1878 were white (> 64%) or black (> 20%). Study 1961 enrolled a more racially diverse population: white (28%), Asian (20%), and black (> 35%) patients. Patients in Study 1844 were largely asymptomatic (> 86%), and > 9% were diagnosed with AIDS. Patients in Study 1878 were also largely asymptomatic (> 81%), and > 11% were diagnosed with AIDS. Women in Study 1961 were also largely asymptomatic (> 89%), and a very small proportion were diagnosed with AIDS (≤ 3%). Eligibility with respect to AIDS is discussed in the previous discussion of studies enrolling treatment-naive patients. All patients enrolled in Study 1844 were receiving ABC/DTG/3TC or DTG + 3TC/ABC, as required by the inclusion criteria. In Study 1878, the most common current ARV regimen at screening was boosted DRV + FTC/TDF, followed by boosted ATV + FTC/TDF. In Study 1961, the most common current ARV was E/C/FTC/TAF (53%) (Table 8).

Table 7: Summary of Baseline Characteristics: Treatment-Naive

Baseline Characteristics		Study 1489		Study 1490	
		B/FTC/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/FTC/TAF (N = 320)	DTG + FTC/TAF (N = 325)
Age (years)	Mean (SD)	34 (10.9)	34 (10.8)	37 (12.3)	37 (11.6)
	Median (range)	31 (18 to 71)	32 (18 to 68)	33 (18 to 71)	34 (18 to 77)
Sex, n (%)	Male	285 (90.8)	282 (89.5)	280 (87.5)	288 (88.6)
	Female	29 (9.2)	33 (10.5)	40 (12.5)	37 (11.4)
Race, n (%)	White	180 (57.7)	179 (56.8)	183 (57.2)	195 (60.0)
	Asian	6 (1.9)	10 (3.2)	7 (2.2)	10 (3.1)
	Black	114 (36.5)	112 (35.6)	97 (30.3)	100 (30.8)
	Other	9 (2.9)	8 (2.5)	33 (10.3)	20 (6.2)
Weight (kg)	Mean (SD)	80.1 (17.7)	80.3 (18.4)	79.1 (17.54)	80.3 (20.68)
BMI (kg/m^2)	Mean (SD)	25.9 (5.3)	26.1 (5.7)	25.8 (5.03)	26.2 (6.25)
Baseline HIV-1 RNA (copies/mL), n (%)	≤ 100,000	261 (83.1)	265 (84.1)	254 (79.4)	271 (83.4)
	> 100,000 to ≤ 400,000	45 (14.3)	38 (12.1)	54 (16.9)	41 (12.6)
	> 400,000	8 (2.5)	12 (3.8)	12 (3.8)	13 (4.0)
eGFR by Cockcroft–Gault (mL/min)	Mean (SD)	131.0 (39.44)	128.8 (33.32)	122.8 (31.59)	129.2 (40.57)
HIV Disease Status, n (%)	Asymptomatic	286 (91.1)	286 (90.8)	286 (89.4)	288 (88.6)
	Symptomatic HIV Infection	16 (5.1)	14 (4.4)	10 (3.1)	11 (3.4)
	AIDS	12 (3.8)	15 (4.8)	24 (7.5)	26 (8.0)
HIV/HBV coinfection status, n (%)	Yes	0	0	8 (2.5)	6 (1.9)
	No	313 (100.0)	312 (100.0)	310 (97.5)	318 (98.1)
	Missing, n	1	3	2	1
HIV/HCV coinfection status, n (%)	Yes	0	4 (1.3)	5 (1.6)	5 (1.5)
	No	313 (100.0)	311 (98.7)	315 (98.4)	320 (98.5)
	Missing, n	1	0	0	0
CD4 counts (/μL)	Mean (SD)	453 (220.8)	476 (231.4)	457 (255.3)	454 (231.5)

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BMI = body mass index; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; FTC/TAF = emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = HIV type 1; RNA = ribonucleic acid; SD = standard deviation.

Source: Clinical Study Report Study1489,[6] Clinical Study Report Study 1490.[7]

Table 8: Summary of Baseline Characteristics: Treatment-Experienced/Switch

Baseline Characteristics		Study 1844		Study 1878		Study 1961	
		B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC) (N = 287)	B/FTC/TAF (N = 234)	SBR (E/C/FTC/TAF or E/C/FTC/TDF or ATV + RTV + FTC/TDF) (N = 236)
Age (years)	Mean (SD)	46 (11.1)	45 (11.5)	47 (10.5)	46 (10.5)	[redacted]	[redacted]
	Median (range)	47 (21 to 71)	45 (20 to 70)	48 (20 to 74)	47 (21 to 79)	39 (21 to 63)	40 (20 to 63)
Sex, n (%)	Male	247 (87.6)	252 (89.7)	243 (83.8)	234 (81.5)	0	0
	Female	35 (12.4)	29 (10.3)	47 (16.2)	53 (18.5)	234 (100.0)	236 (100.0)
Race, n (%)	White	206 (73.0)	202 (72.7)	188 (64.8)	190 (66.2)	66 (28.2)	67 (28.4)
	Asian	9 (3.2)	9 (3.2)	6 (2.1)	10 (3.5)	48 (20.5)	54 (22.9)
	Black	59 (20.9)	62 (22.3)	79 (27.2)	72 (25.1)	91 (38.9)	83 (35.2)
	Other	6 (2.1)	6 (2.1)	17 (5.9)	15 (5.2)	29 (12.4)	32 (13.6)
Weight (kg)	Mean (SD)	83.7 (18.5)	83.8 (18.3)	82.2 (14.89)	81.4 (18.59)	[redacted]	[redacted]
BMI (kg/m^2)	Mean (SD)	27.3 (5.9)	27.1 (5.3)	27.0 (4.97)	27.0 (6.13)	[redacted]	[redacted]
Baseline HIV-1 RNA (copies/mL), n (%)	< 50 copies/mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 50 copies/mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	< 20 copies/mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR by Cockcroft–Gault (mL/min)	Mean (SD)	104.3 (32.2)	104.9 (30.8)	109.9 (30.97)	108.4 (31.75)	[redacted]	[redacted]
HIV disease status, n (%)	Asymptomatic	243 (86.2)	245 (87.2)	240 (82.8)	234 (81.5)	209 (89.3)	216 (91.5)
	Symptomatic HIV infection	9 (3.2)	9 (3.2)	16 (5.5)	20 (7.0)	18 (7.7)	15 (6.4)
	AIDS	30 (10.6)	27 (9.6)	34 (11.7)	33 (11.5)	[redacted]	[redacted]
HIV/HBV coinfection status, n (%)	Yes	0	0	8 (2.8)	6 (2.1)	5 (2.1)	2 (0.9)
	No	282 (100.0)	281 (100.0)	278 (97.2)	280 (97.9)	229 (97.9)	232 (99.1)
	Missing, n	NA	NA	4	1	0	2
HIV/HCV coinfection status, n (%)	Yes	0	1 (0.4)	5 (1.7)	5 (1.7)	5 (2.1)	7 (3.0)
	No	282 (100.0)	280 (99.6)	283 (98.3)	282 (98.3)	229 (97.9)	229 (97.0)
	Missing, n	NA	NA	2	0	NA	NA
ART at screening by regimen (> 5% in either group), n (%)	Boosted ATV + ABC/3TC	NA	NA	21 (7.2)	23 (8.0)	NA	NA
	Boosted DRV + ABC/3TC	NA	NA	24 (8.3)	21 (7.3)	NA	NA
	Boosted ATV + FTC/TDF	NA	NA	105 (36.2)	110 (38.3)	NA	NA
	Boosted DRV + FTC/TDF	NA	NA	140 (48.3)	133 (46.3)	NA	NA

Baseline Characteristics		Study 1844		Study 1878		Study 1961	
		B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC) (N = 287)	B/FTC/TAF (N = 234)	SBR (E/C/FTC/TAF or E/C/FTC/TDF or ATV + RTV + FTC/TDF) (N = 236)
	E/C/FTC/TAF	NA	NA	NA	NA	124 (53.0)	125 (53.0)
	E/C/FTC/TDF	NA	NA	NA	NA	99 (42.3)	98 (41.5)
	RTV-boosted ATV + FTC/TDF	NA	NA	NA	NA	11 (4.7)	13 (5.5)
CD4 counts	Mean (SD)	752 (302.2)	694 (291.6)	669 (303.4)	657 (285.0)	[redacted]	[redacted]

ABC/3TC = abacavir/lamivudine; ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; ART = antiretroviral therapy; ATV = atazanavir; B/FTC/TAF = bictegravir/emtricitabine/ tenofovir alafenamide; BMI = body mass index; DRV = darunavir; E/C/FTC/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; E/C/FTC/TDF = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; eGFR = estimated glomerular filtration rate; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = HIV type 1; NA = not applicable; RNA = ribonucleic acid; RTV = ritonavir; SBR = stay on baseline regimen; SD = standard deviation.

Source: Clinical Study Report Study 1844,[8] Clinical Study Report Study 1878,[9] Clinical Study Report Study 1961.[10]

Interventions

Treatment-Naive

Patients in Study 1489 were randomly assigned 1:1 to receive either B/FTC/TAF (50 mg/200 mg/25 mg) fixed-dose combination (FDC) + placebo-to-match ABC/DTG/3TC (600 mg/50 mg/300 mg) FDC administered orally, once daily, without regard to food; or to ABC/DTG/3TC (600 mg/50 mg/300 mg) FDC + placebo-to-match B/FTC/TAF (50 mg/200 mg/25 mg) FDC administered orally, once daily, without regard to food, for 144 weeks. This was a double-blind study.

Patients in Study 1490 were randomly assigned 1:1 to receive either B/FTC/TAF (50 mg/200 mg/25 mg) FDC + placebo-to-match DTG (50 mg) and placebo-to-match FTC/TAF (200 mg/25 mg) FDC administered orally, once daily, without regard to food; or to DTG (50 mg) and FTC/TAF (200 mg/25 mg) FDC + placebo-to-match B/FTC/TAF (50 mg/200 mg/25 mg) FDC administered orally, once daily, without regard to food for 144 weeks. This was a double-blind study.

Treatment-Experienced/Switch

Patients in Study 1844 (virologically suppressed on a stable regimen of DTG + ABC/3TC or ABC/DTG/3TC FDC) were randomly assigned 1:1 to receive either B/FTC/TAF (50 mg/200 mg/25 mg) FDC + placebo-to-match ABC/DTG/3TC (600 mg/50 mg/300 mg) FDC administered orally, once daily, without regard to food or to ABC/DTG/3TC (600 mg/50 mg/300 mg) FDC + placebo-to-match B/FTC/TAF (50 mg/200 mg/25 mg) FDC administered orally, once daily, without regard to food, for a minimum of 48 weeks. This was a double-blind study.

Patients in Study 1878 were randomly assigned 1:1 to receive an open-label regimen of either B/FTC/TAF (50 mg/200 mg/25 mg) FDC orally once daily, without regard to food, or to remain on their current ARV regimen, consisting of ritonavir (RTV)- or cobicistat (COBI)-

boosted atazanavir (ATV) or darunavir (DRV) + either FTC/tenofovir disoproxil fumarate (TDF) or ABC/3TC, administered orally once daily with food, for a minimum of 48 weeks.

Women in Study 1961 were randomly assigned 1:1 to receive an open-label regimen of either B/FTC/TAF (50 mg/200 mg/25 mg) FDC orally once daily, without regard to food, or to remain on their current ARV regimen, consisting of E/C/FTC/TAF, E/C/FTC/TDF, or ATV + RTV + FTC/TDF, administered orally once daily with food, for a minimum of 48 weeks.

In all five studies, patients refrained from consuming grapefruit juice and Seville orange juice throughout the study. In addition to the medications listed in the exclusion criteria, participants could not take sucralfate, antacids, or vitamin or mineral supplements containing calcium, iron, or zinc for a minimum of six hours before or two hours after any dose of study drug. In addition, if metformin use was necessary, close monitoring was recommended.

Outcomes

Treatment-Naive

The primary outcome in Study 1489 and Study 1490 was the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48, as determined by the US FDA-defined snapshot algorithm in the full analysis set (FAS) population.

Secondary outcomes of interest were identified in the review protocol: virologic failure, resistance, study drug adherence, and health-related quality of life (HRQoL). Virologic failure was defined as the proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48, as determined by the US FDA-defined snapshot algorithm. Genotyping and phenotyping of integrase, protease, and reverse transcriptase was performed for any patient who, after achieving HIV-1 RNA < 50 copies / mL, experienced either (1) a rebound in HIV-1 RNA ≥ 50 copies/mL at any visit, or (2) at any visit, a > 1 log10 increase in HIV-1 RNA from the nadir and a confirmed HIV-1 RNA ≥ 200 copies/mL. Resistance testing was also performed for any patient who had an HIV-1 RNA ≥ 200 copies/mL at week 48 or at the last visit on study drug, which was subsequently confirmed at the following scheduled or unscheduled visit.

Study drug adherence was calculated based on pill counts for active drug only. Study regimen adherence was computed as the numbers of pills taken divided by the numbers of pills prescribed. The numbers of pills of study drugs dispensed and returned were captured on study drug accountability forms.

HRQoL was measured using the Short Form (36) Health Survey (SF-36) and was completed by the patient (self-report) at day 1 (baseline) and weeks 4, 12, and 48.

One subgroup analysis was preplanned in both study protocols: primary efficacy outcome by baseline viral load (< 100,000 copies/mL and ≥ 100,000 copies/mL).

Harms outcomes included the monitoring of all adverse events (AEs; recorded using uniform guidelines and graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities), clinical laboratory tests, and dual energy X-ray absorptiometry (DXA) (note: DXA was not measured in Study 1490).

Treatment-Experienced/Switch

The primary outcome in Study 1844, Study 1878, and Study 1961 was the proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48, as determined by the US FDA-defined snapshot algorithm in the FAS population.

The secondary outcomes of interest were identified in the systematic review protocol: virologic success, resistance, study drug adherence, and HRQoL. Virologic success was defined as HIV-1 RNA < 50 copies/mL at week 48, as determined by the US FDA-defined snapshot algorithm. Resistance, study drug adherence (note: in Study 1878 adherence was measured only for the B/FTC/TAF group), and HRQoL were measured and are identical to those described earlier for the treatment-naive population. Study 1961 did not include a measure of HRQoL.

Harms outcomes included the monitoring of all AEs, clinical laboratory tests, and DXA (note: DXA was not measured in Study 1878 or Study 1961).

Statistical Analysis

Treatment-Naive

Study 1489 and 1490 were both noninferiority trials. For both trials, the estimated sample size was 600 patients (300 patients per treatment group), assuming 95% power to detect a noninferiority margin of 12% at the week 48 response rate (HIV-1 RNA < 50 copies/mL, as determined by the US FDA-defined snapshot algorithm) difference between the two treatment groups. For sample size and power calculations, it was assumed that each treatment group would have a response rate of 91%, the noninferiority margin was 12%, and the significance level was 0.025 (one-sided). The primary outcome (difference in response rate) was calculated based on Mantel–Haenszel proportion and adjusted by baseline HIV-1 RNA level.

Although both studies were designed with follow-up to week 144, the pre-specified primary analysis is at week 48. The primary analysis set for efficacy analyses is the FAS. Efficacy analysis included HIV-1 RNA level (≤ 100,000 versus > 100,000 copies/mL) and region (US versus outside the US).

In both studies, two interim Independent Data Monitoring Committee (IDMC) analyses were performed before the analysis of the primary end point (at week 48), and an alpha penalty of 0.00001 was applied for each interim analysis. Therefore, the alpha level for the primary end point was adjusted to 0.04998 (corresponding to 95.002% confidence interval). The alpha level was only adjusted for the primary end point.

For both Study 1489 and Study 1490, two approaches to missing data were used to analyze the primary outcome: Missing = Failure and Missing = Excluded. In the Missing = Failure approach, all missing data were treated as HIV-1 RNA ≥ 50 copies/mL. The denominator for percentages was the number of subjects in the FAS. In the Missing = Excluded approach, all missing data were excluded from the computation of the percentages (i.e., missing data points were excluded from both the numerator and denominator).

Other efficacy outcomes: Subgroup analysis using HIV-1 RNA level (≤ 100,000 or > 100,000 copies/mL), the proportion difference between the two treatment groups, and the 95% confidence interval (CI) were computed using Mantel–Haenszel proportions adjusted

by region. The percentage change from baseline to week 48 in hip bone mineral density (BMD) and spine BMD was compared between the two treatment groups using analysis of variance (ANOVA) (treatment as a fixed effect). Changes from baseline to week 48 in serum creatinine and eGFR were estimated from a two-sided Wilcoxon rank sum test. Change from baseline to week 48 in SF-36 subscales (physical component summary [PCS] and mental component summary [MCS]) were compared between treatment groups using a two-sided Wilcoxon rank sum test.[31] Alpha was not adjusted to reflect multiple comparisons.

Treatment-Experienced/Switch

Study 1844: A total of approximately 520 HIV-infected subjects, randomized in a 1:1 ratio to two treatment groups (260 subjects per treatment group) achieves at least 90% power to detect a noninferiority margin of 4% difference in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL at week 48 between the two treatment groups. For the sample size and power computation, it is assumed that both treatment groups have 2% of subjects with HIV-1 RNA ≥ 50 copies/mL at week 48, the noninferiority margin is 4%, and the significance level of the test is at a one-sided 0.025 level. The point estimate of treatment difference (B/FTC/TAF group – ABC/DTG/3TC group) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL and the associated two-sided 95.002% CI were constructed based on an unconditional exact method using two inverted one-sided tests.

The primary analysis set for efficacy analyses is the FAS. There were no strata in the randomization, and none were included in the analysis.

Two interim IDMC analyses were performed before the analysis of the primary end point (proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48), and an alpha penalty of 0.00001 was applied for each interim analysis. Therefore, the alpha level for the primary end point was adjusted to 0.04998 (corresponding to 95.002% CI). The alpha level was also adjusted to 0.04998 for the key secondary efficacy end point (proportion of patient switch HIV-1 RNA < 50 copies/mL at week 48). The alpha level was not adjusted for any additional end points.

Two approaches to missing data were used to analyze the primary outcome: Missing = Failure and Missing = Excluded. In the Missing = Failure approach, all missing data were treated as HIV-1 RNA ≥ 50 copies/mL. The denominator for percentages was the number of subjects in the FAS. In the Missing = Excluded approach, all missing data were excluded from the computation of the percentages (i.e., missing data points were excluded from both the numerator and denominator).

Other efficacy outcomes: The point estimate of treatment difference (B/FTC/TAF group – ABC/DTG/3TC group) in the percentage of patients with HIV-1 RNA < 50 copies/mL and the associated two-sided 95.002% CI were constructed based on an unconditional exact method using two inverted one-sided tests. The percentage change from baseline to week 48 in hip BMD and spine BMD was compared between the two treatment groups using ANOVA (treatment as a fixed effect). Changes from baseline to week 48 in serum creatinine and eGFR were estimated from a two-sided Wilcoxon rank sum test. Change from baseline to week 48 in SF-36 subscales (PCS and MCS) were compared between treatment groups using a two-sided Wilcoxon rank sum test.[31] Alpha was not adjusted to reflect multiple comparisons.

Study 1878: A total of approximately 520 HIV-infected subjects, randomized in a 1:1 ratio to two treatment groups (260 subjects per treatment group) achieves at least 90% power to detect a noninferiority margin of 4% difference in the percentage of subjects with HIV-1

RNA ≥ 50 copies/mL at week 48 between the two treatment groups. For the sample size and power computation, it is assumed that both treatment groups have 2% of subjects with HIV-1 RNA ≥ 50 copies/mL at week 48, that the noninferiority margin is 4%, and that the significance level of the test is at a one-sided 0.025 level. The point estimate of treatment difference (B/FTC/TAF group – stay on baseline regimen [SBR] group) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL and the associated two-sided 95.002% CI were constructed based on an unconditional exact method using two inverted one-sided tests.

The primary analysis set for efficacy analyses is the FAS. Although randomization was stratified by prior treatment-regimen group (i.e., TDF-containing regimens and non–TDF-containing regimens), no strata were included in the analysis, and subgroup results based on SBR were not provided.

Two interim IDMC analyses were performed before the analysis of the primary end point (proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48), and an alpha penalty of 0.00001 was applied for each interim IDMC analysis. Therefore, the alpha level for the primary end point was adjusted to 0.04998 (corresponding to 95.002% confidence interval). The alpha level was also adjusted to 0.04998 for the key secondary efficacy end point (proportion of patient switch HIV-1 RNA < 50 copies/mL at week 48). The alpha level was not adjusted for any additional end points.

Two approaches to missing data were used to analyze the primary outcome: Missing = Failure and Missing = Excluded. In the Missing = Failure approach, all missing data were treated as HIV-1 RNA ≥ 50 copies/mL. The denominator for percentages was the number of subjects in the FAS. In the Missing = Excluded approach, all missing data were excluded from the computation of the percentages (i.e., missing data points were excluded from both the numerator and denominator).

Other efficacy outcomes: The point estimate of treatment difference (B/FTC/TAF group – SBR group) in the percentage of patients with HIV-1 RNA < 50 copies/mL and the associated two-sided 95.002% CI were constructed based on an unconditional exact method using two inverted one-sided tests. Changes from baseline to week 48 in serum creatinine and eGFR were estimated from a two-sided Wilcoxon rank sum test. Alpha was not adjusted to reflect multiple comparisons.

Study 1961: The statistical analysis plan for Study 1961 was not provided by the manufacturer. A total of approximately 470 HIV-infected women, randomized in a 1:1 ratio to two treatment groups (approximately 235 subjects per treatment group) was planned to achieve at least 87% power to detect a noninferiority margin of 4% difference in week 48 response rate (HIV-1 RNA ≥ 50 copies/mL as determined by the US FDA-defined snapshot algorithm) between the two treatment groups. For sample size and power computation, it was assumed that both treatment groups had 2% of subjects with HIV-1 RNA ≥ 50 copies/mL at week 48, that the noninferiority margin was 4%, and that the significance level of the test was at a one-sided 0.025 level. It is noted that the Protocol Amendment 2 (10 November 2016) states: “Revised the sample size and power calculation to reflect enrolment of approximately 470 subjects total.”[10] The point estimate of treatment difference (B/FTC/TAF group –SBR group) in the percentage of patients with HIV-1 RNA ≥ 50 copies/mL and the associated two-sided 95.001% CI were constructed based on an unconditional exact method using two inverted one-sided tests.

The primary analysis set for efficacy analyses was the FAS. Although randomization was stratified by baseline regimen (E/C/FTC/TAF, E/C/FTC/TDF, or ATV + RTV + FTC/TDF), no strata were included in the analysis, and no subgroup results based on SBR were provided.

One interim IDMC analyses was performed before the analysis of the primary end point (proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48), and an alpha penalty of 0.00001 was applied for each interim IDMC meeting. Therefore, the alpha level for the primary end point was adjusted to 0.04999 (corresponding to 95.001% CI). The alpha level was also adjusted to 0.04999 for the key secondary efficacy end point (proportion of patient switch HIV-1 RNA < 50 copies/mL at week 48). The alpha level was not adjusted for any additional end points.

Two approaches to missing data were used to analyze the primary outcome: Missing = Failure and Missing = Excluded. In the Missing = Failure approach, all missing data were treated as HIV-1 RNA ≥ 50 copies/mL. The denominator for percentages was the number of subjects in the FAS. In the Missing = Excluded approach, all missing data were excluded from the computation of the percentages (i.e., missing data points were excluded from both the numerator and denominator).

Other efficacy outcomes: The point estimate of treatment difference (B/FTC/TAF group – SBR group) in the percentage of patients with HIV-1 RNA < 50 copies/mL and the associated 2-sided 95.002% CI were constructed based on an unconditional exact method using two inverted one-sided tests. Changes from baseline to week 48 in serum creatinine and eGFR were estimated from a two-sided Wilcoxon rank sum test. Alpha was not adjusted to reflect multiple comparisons.

Analysis Populations

The analysis sets are defined identically in all five trials (two treatment-naive studies, three treatment-experienced/switch studies; Table 9). The primary analysis set for the efficacy analyses in all five trials was the FAS. The FAS included all patients who were randomized into the study and received at least one dose of the study drug. The FAS differs from the intention-to-treat analysis set (called “all randomized analysis set” in each of the five trials) because the FAS includes the additional criteria of “receiving at least one dose of study drug.”

Table 9: Analysis Populations in the Included Clinical Trials

Analysis Set	Description
Study 1489, 1490, 1844, 1878, 1961	
All randomized analysis set	Included all subjects randomized into the study.
FAS	Included all patients who: 1. were randomized into the study, and 2. received at least 1 dose of study drug.
PP analysis set	Included all subjects who: 1. were randomized into the study, 2. received at least 1 dose of study drug, and 3. had no major protocol violation, including the violation of key entry criteria.
Safety	Included all subjects who: 1. were randomized into the study, and 2. received at least 1 dose of study drug.

FAS = full analysis set; PP = per-protocol.

Source: Clinical Study Report Study1489,[6] Clinical Study Report Study 1490,[7] Clinical Study Report Study 1844,[8] Clinical Study Report Study 1878,[9] Clinical Study Report Study 1961.[10]

Patient Disposition

Treatment-Naive

Patient disposition for Study 1489 and 1490 is displayed in Table 10. Study 1489 and 1490 randomized 631 and 657 patients, respectively. A similar proportion of patients in both trials completed 48 weeks. In Study 1489, 94.3% of patients randomized to B/FTC/TAF and 95.6% of patients randomized to ABC/DTG/3TC completed the study at 48 weeks. In Study 1490, 92.5% of patients randomized to B/FTC/TAF and 94.5% of patients randomized to DTG + FTC/TAF completed 48 weeks. The most common reasons for study discontinuation were loss to follow-up and withdrawn consent.

There are discrepancies between the number of patients randomized (i.e., all randomized analysis set) and the FAS. In Study 1489, two patients were randomized to B/FTC/TAF but withdrew consent before receiving the first dose. In Study 1490, seven patients randomized to B/FTC/TAF and five patients randomized to DTG+FTC/TAF did not receive study drugs (four due to withdrawn consent, three due to investigator's discretion, three due to loss of follow-up, and two due to protocol violation).

Treatment-Experienced

Patient disposition for Study 1844, 1878, and 1961 is shown in Table 11. The proportion of patients completing 48 weeks was numerically higher in Study 1961 (B/FTC/TAF: 99%, SBR: 98%) compared with Study 1844 (B/FTC/TAF: 97%, ABC/DTG/3TC: 96%) and Study 1878 (B/FTC/TAF: 96%, SBR: 93%). This may reflect the population eligible for Study 1961 — all women were previously enrolled in selected trials conducted by the manufacturer. Withdrawal of consent was the most common cause of study discontinuation in Study 1844 (B/FTC/TAF: 1.1%, ABC/DTG/3TC: 2.5%) and Study 1878 (B/FTC/TAF: 2.8%, SBR: 4.9%).

There are discrepancies between the number of patients randomized (i.e., all randomized analysis set) and the FAS. In Study 1844, two patients randomized to B/FTC/TAF and two patients randomized to ABC/DTG/3TC did not receive study drugs due to withdrawn consent or protocol violation. In Study 1878, one patient randomized to the SBR group never received treatment with the study drug due to a protocol violation. In Study 1961, one patient randomized to B/FTC/TAF did not receive the study drug due to pregnancy, and one patient randomized to SBR did not receive the study drug due to withdrawal of consent.

Table 10: Patient Disposition at 48 Weeks: Treatment-Naive

Patient Disposition	Study 1489		Study 1490	
	B/FTC/TAF	ABC/DTG/3TC	B/FTC/TAF	DTG + FTC/TAF
Screened, N	739		742	
Randomized, N (%)	631		657	
Per treatment arm	316	315	327	330
FAS	314 (99.4)	315 (100.0)	320 (97.9)	325 (98.5)
PP population	289 (91.5)	293 (93.0)	282 (86.2)	297 (90.0)
Safety population	314 (99.4)	315 (100.0)	320 (97.9)	325 (98.5)
Completed 48 weeks, N (%)	296 (94.3)	301 (95.6)	296 (92.5)	307 (94.5)
Discontinued study before 48 weeks, N (%)	18 (5.7)	14 (4.4)	24 (7.5)	18 (5.5)
Adverse event	0	3 (1.0)	3 (0.9)	1 (0.3)
Death	0	0	1 (0.3)	2 (0.6)

Patient Disposition	Study 1489		Study 1490	
	B/FTC/TAF	ABC/DTG/3TC	B/FTC/TAF	DTG + FTC/TAF
Pregnancy	0	0	0	0
Investigator discretion	3 (1.0)	0	3 (0.9)	0
Lack of efficacy	0	0	0	0
Lost to follow-up	9 (2.9)	6 (1.9)	8 (2.5)	5 (1.5)
Protocol violation	1 (0.3)	0	2 (0.6)	1 (0.3)
Noncompliance	2 (0.6)	0	0	1 (0.3)
Withdrawn consent	3 (1.0)	5 (1.6)	7 (2.2)	8 (2.5)

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; FTC/TAF = emtricitabine/tenofovir alafenamide; FAS = full analysis set; PP = per-protocol.

Source: Clinical Study Report Study1489,[6] Clinical Study Report Study 1490.[7]

Table 11: Patient Disposition at 48 Weeks: Treatment-Experienced/Switch

Patient Disposition	Study 1844		Study 1878		Study 1961	
	B/FTC/TAF	ABC/DTG/3TC	B/FTC/TAF	SBR	B/FTC/TAF	SBR
Screened, N	646		707		491	
Randomized, N (%)	567		578		472	
Per treatment arm	284	283	290	288[b]	235[b]	237[b]
FAS	282 (99.3)	281 (99.3)	290 (100.0)	287 (99.7)	234 (99.6)	236 (99.6)
PP population	257 (90.5)	256 (90.5)	269 (92.8)	250 (86.8)	224 (95.3)	222 (93.7)
Safety population	282 (99.3)	281 (99.3)	290 (100.0)	287 (99.7)	234 (99.6)	236 (99.6)
Completed 48 weeks, N (%)	272 (96.5%)	269 (95.7%)	277 (95.5%)[a]	267 (93.0%)[a]	231 (98.7%)[b]	231 (97.9%)[b]
Discontinued study before 48 weeks, N (%)	10 (3.5)	12 (4.3)	13 (4.5)	20 (7.0)	3 (1.3)	5 (2.1)
Adverse event	3 (1.1)	2 (0.7)	2 (0.7)	0	0	0
Death	2 (0.7)	0	1 (0.3)	1 (0.3)	0	1 (0.4)
Pregnancy	0	1 (0.4)	0	0	3 (1.3)	1 (0.4)
Investigator discretion	0	0	0	1 (0.3)	0	2 (0.8)
Lack of efficacy	0	0	0	0	0	0
Lost to follow-up	2 (0.7)	2 (0.7)	0	3 (1.0)	0	1 (0.4)
Protocol violation	0	0	1 (0.3)	0	0	0
Noncompliance	0	0	1 (0.3)	1 (0.3)	0	0
Withdrawn consent	3 (1.1)	7 (2.5)	8 (2.8)	14 (4.9)	0	0

ABC/DTG/3TC = abacavir/dolutegravir /lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; FAS = full analysis set; PP = per-protocol; SBR = stay on baseline regimen.

[a] B/FTC/TAF = [redacted] = [redacted] (patients who have completed 48 weeks but are still on study in the randomized phase) + [redacted] (patients who have completed 48 weeks and completed the randomized phase); SBR = [redacted] = [redacted] (patients who have completed 48 weeks but are still on study in the randomized phase) + [redacted] (patients who have completed 48 week and completed the randomized phase).

[b] B/FTC/TAF = [redacted] = [redacted] (patients who have completed 48 weeks but are still on study in the randomized phase) + [redacted] (patients who have completed 48 weeks and completed the randomized phase); SBR = [redacted] = [redacted] (patients who have completed 48 weeks but are still on study in the randomized phase) + [redacted] (patients who have completed 48 week and completed the randomized phase).

Source: Clinical Study Report Study 1844,[8] Clinical Study Report Study 1878,[9] Clinical Study Report Study 1961.[10]

Exposure to Study Treatments

All five studies are currently ongoing, with the cut point for the provided data being when all randomized subjects had completed the week 48 visit or had prematurely discontinued study drugs before their week 48 visit.

[redacted]

Table 12: Exposure to Study Treatments at Data Cut Point (Safety Set): Treatment-Naive

Exposure	Study 1489		Study 1490	
	B/FTC/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/FTC/TAF (N = 320)	DTG + FTC/TAF (N = 325)
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of Exposure to Study Drug, n (%)				
≥ 4 weeks (28 days)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 8 weeks (56 days)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 weeks (84 days)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 24 weeks (168 days)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 36 weeks (252 days)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 48 weeks (336 days)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 60 weeks (420 days)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 72 weeks (504 days)	[redacted]	[redacted]	[redacted]	[redacted]

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; FTC/TAF = emtricitabine/tenofovir alafenamide; SD = standard deviation.

[redacted]

Source: Clinical Study Report Study1489,[6] Clinical Study Report Study 1490.[7]

Table 13: Exposure to Study Treatments at Data Cut Point (Safety Set): Treatment-Experienced/Switch

Exposure	Study 1844		Study 1878		Study 1961	
	B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (N = 287)	B/FTC/TAF (N = 234)	SBR (N = 236)
Duration of Exposure to Study Drug (Weeks)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of Exposure to Study Drug, n (%)						
≥ 4 weeks (28 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 8 weeks (56 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 weeks (84 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 24 weeks (168 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 36 weeks (252 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 48 weeks (336 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 60 weeks (420 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 72 weeks (504 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; NA = not applicable; SBR = stay on baseline regimen; SD = standard deviation.

[redacted]

Source: Clinical Study Report Study 1844,[8] Clinical Study Report Study 1878,[9] Clinical Study Report Study 1961.[10]

Critical Appraisal

Internal Validity

Treatment-Naive (Study 1489 and Study 1490)

Study 1489 and Study 1490 were randomized, double-blind, double-dummy trials. Selection bias (random sequence generation) was minimized, as there was adequate generation of a randomized sequence. Randomization was centralized and computer-generated. Once eligibility was confirmed, the investigator or designee randomized patients using the interactive Web response system. A third party provided interactive Web response system data and stored the results electronically on its server. Patients were randomized 1:1 (block size four) to the treatment arms. Both trials concealed treatment allocation before treatment assignment (third-party central allocation), thus minimizing selection bias. Both patients and study personnel were blinded to treatment allocation, minimizing the risk of performance bias. Study personnel responsible for outcome assessment were blinded to treatment allocation, minimizing the risk of detection bias.

The primary outcome (proportion of patients with HIV-1 RNA < 50 copies/mL) is an objective outcome measure (blood draw) and therefore less susceptible to bias. The

operational definition of the primary outcome and the noninferiority margin of 12% are consistent with the guidance from the US FDA using the snapshot algorithm.

The sample size target for both studies was 600 (randomized 1:1 to two treatment groups) and was achieved by both studies (Study 1489: n = 631, Study 1490: n = 657). The sample size calculation estimated that the study would have 95% power to detect noninferiority (margin –12%). Furthermore, the calculation assumed that 91% of patients in both treatment groups would achieve an HIV-1 RNA < 50 copies/mL at week 48. This was achieved in Study 1489. However, in Study 1490, 89% of the B/FTC/TAF group achieved HIV-1 RNA < 50 copies/mL at week 48. Appropriate adjustment to the *P* value for the primary outcome was made to reflect two interim analyses conducted before the primary analysis at week 48. Each interim analysis incurred a penalty of 0.001; thus, the CI was adjusted from 95% to 95.002%. No adjustments were made to alpha for the analysis of secondary outcomes. These results should be considered exploratory.

Losses to follow-up were disclosed, and there was no evidence of differential attrition between treatment groups within each study. Two methods were used handle missing data in the analysis of the primary outcome: Missing = Failure and Missing = Excluded. For both studies, Missing = Failure and Missing = Excluded analyses were consistent with the FAS analysis of the primary outcome.

Adherence was either similar or slightly higher for B/FTC/TAF than for the comparator groups in the included trials. Adherence to the study treatments, therefore, may not affect the overall conclusion of noninferiority of the B/FTC/TAF compared with comparators. There was no considerable difference in early withdrawal or discontinuation of the treatment in all included studies. Therefore, it is unlikely that this would impact the findings.

Noninferiority trials assume constancy — that is, that the control versus placebo effect has not changed over time. However, it is unknown whether the efficacy of the control group (i.e., Study 1489: ABC/DTG/3TC, Study 1490: DTG + FTC/TAF) would demonstrate the same treatment effect as was seen in the original placebo-controlled trials, particularly when the treatment patterns may have evolved.

Treatment-Experienced/Switch (Study 1844, 1878, 1961)

Study 1844, Study 1878, and Study 1961 are randomized trials. Study 1844 is double-blind, double-dummy, and Study 1878 and Study 1961 are open-label. There was adequate generation of the random sequence and randomization was centralized (third party), thus minimizing the risk of selection bias. There was adequate concealment of treatment allocation before treatment assignment, thus minimizing the risk of selection bias. Performance bias was minimized in Study 1844, as both investigators and patients were blinded to treatment assignment.

Study 1844 was double-blind (participants, study personnel, and outcome assessors) and at low risk of detection bias. In addition, the primary outcome of interest (plasma HIV-1 RNA, in copies/mL) was an objective outcome measure. Study 1878 and Study 1961 were open-label — both patients and investigators were aware of treatment assignment. However, the primary outcome (plasma HIV-1 RNA, in copies/mL) is an objective outcome measure, and differential measurement is minimized despite lack of blinding of the patient and investigator.

Study 1844 was double-blind, thus minimizing attrition bias. There were no observed differences in withdrawals from the study between groups. Study 1878 and Study 1961

were open-label and at risk of attrition bias. However, differences in attrition were not observed between treatment groups in either study. Losses to follow-up were disclosed, and there was no evidence of differential attrition between treatment groups within each study. Two methods were used handle missing data in the analysis of the primary outcome: Missing = Failure and Missing = Excluded. For both studies, Missing = Failure and Missing = Excluded analyses were consistent with the FAS analysis of the primary outcome.

The sample size target for Study 1844 and 1878 was 520 (randomized 1:1 to two treatment groups) and was achieved by Study 1844 and Study 1878 (Study 1844: n = 567, Study 1878: n = 578). The sample size calculation assumed that, in both treatment groups, 2% of patients would have HIV-1 RNA ≥ 50 copies/mL at week 48. In Study 1848 and Study 1878, ≤ 2% of patients had HIV-1 RNA ≥ 50 copies/mL at week 48. In Study 1961, the enrolment target was 470 (randomized 1:1 to two treatment groups) and was achieved (n = 472). However, in Protocol Amendment 2, the sample size and power calculation were revised to "reflect enrolment of approximately 470 subjects total." It is unclear why the sample size was revised.

The primary outcome in all three studies (proportion of patients with HIV-1 RNA ≥ 50 copies/mL) is an objective outcome measure (blood draw) and therefore less susceptible to bias. The operational definition of the primary outcome and the noninferiority margin of 4% are consistent with the guidance from the US FDA, using the snapshot algorithm.

For all studies, appropriate adjustment to the *P* value for the primary outcome was made to reflect two interim analyses conducted before the primary analysis at week 48. Each interim analysis incurred a penalty of 0.001; thus, the CI was adjusted from 95% to 95.002%. No adjustments were made to alpha for the analysis of secondary outcomes, and it should therefore be considered exploratory.

Noninferiority trials assume constancy — that is, that the control versus placebo effect has not changed over time. However, it is unknown whether the efficacy of the treatments in the control group would demonstrate the same treatment effect as was seen in the original placebo-controlled trials, particularly when the treatment patterns may have evolved.

External Validity

Treatment-Naive

Study 1489 and Study 1490 enrolled patients from a range of countries. Study 1489 enrolled patients from Belgium, Canada, Dominican Republic, France, Germany, Italy, Spain, UK, and the US. Study 1490 enrolled patients from Australia, Belgium, Canada, Dominican Republic, France, Germany, Italy, Spain, UK, and the US.

The comparator in Study 1489 (ABC/DTG/3TC, Triumeq) and Study 1490 (DTG + FTC/TAF, Tivicay + Descovy) are both currently used in Canadian practice. Both comparators are recommended initial regimens for people with HIV.[4] The treatments in the comparator group in Study 1489 and Study 1490 were administered at a dosage consistent with the approved indication.

Both studies had strict inclusion and exclusion criteria, making the study patients more likely to respond but less likely to experience AEs than the general population of individuals living with HIV. Study 1489 and Study 1490 largely enrolled white men aged 34 to 37 years with asymptomatic HIV. The majority of patients were not co-infected with HBV (Study 1489: no patients co-infected; Study 1490: B/FTC/TAF group 2.5%, DTG + FTC/TAF 1.9%)

or HCV (Study 1489: B/FTC/TAF no patients co-infected; ABC/DTG/3TC 1.3%; Study 1490: B/FTC/TAF group 1.6%, DTG + FTC/TAF 1.5%) In Canada, it is estimated that women represent approximately 25% of the population with HIV. However, in Study 1489 and 1490, women represent approximately 10% and approximately 12% of the study population. It is unknown whether women responded differently to the treatments in these studies.

In particular, there may be harms, including potential impairment to renal, liver function, or bone density (all study patients were required to have adequate renal function: eGFR ≥ 50 mL/min [≥ 0.83 mL/s] according to the Cockcroft–Gault formula), for patients who do not meet these criteria. It is unknown whether the drug could be used as effectively and safely in patients who were not included in the trials.

Treatment-Experienced/Switch

Study 1844, Study 1878, and Study 1961 enrolled patients from a range of countries. Study 1844 enrolled patients from Australia, Belgium, Canada, France, Germany, Italy, Spain, UK, and the US (including Puerto Rico). Study 1878 enrolled patients from Australia, Belgium, Canada, Dominican Republic, France, Germany, Italy, Spain, UK, and the US. Study 1961 enrolled patients from the Dominican Republic, Russian Federation, Thailand, Uganda, and the US (including Puerto Rico). Patients enrolled in Study 1961 could be eligible to participate if they had previously participated in predefined trials by the manufacturer. It is unclear whether all participants who were eligible to participate were given the opportunity to participate.

The comparators in all studies are currently available for use in Canada: Study 1844 (ABC/DTG/3TC, Triumeq), Study 1878 (boosted ATV or DRV + FTC/TDF or ABC/3TC), and Study 1961 (E/C/FTC/TAF, Genvoya; E/C/FTC/TDF, Stribild; ATV + RTV + FTC/TDF, ATV + RTV + Truvada). The clinical expert consulted for this review noted that the comparators in Study 1878 are older medicines and not frequently used in current practice. The treatments in Study 1844, 1878, and 1961 were administered at a dosage consistent with the approved indication.

Similar to the treatment-naive studies, the treatment-experienced/switch studies had strict inclusion and exclusion criteria, making the study patients more likely to respond but less likely to experience AEs. The patients enrolled in Study 1844, Study 1878, and Study 1961 were older (mean age 40 to 47 years) than the patients enrolled in the treatment-naive studies, which was expected, given that all patients were currently receiving stable ARV treatment before enrolment. All three studies primarily enrolled HIV-asymptomatic patients. Race was heterogenous in Study 1961 (distributed fairly equally among white, Asian, and black ethnic groups). Women represented approximately 11% and 17% of the study population in studies 1844 and 1878, whereas it is estimated that women represent approximately 25% of the population with HIV in Canada. However, Study 1961, which exclusively enrolled women, provides additional evidence relevant to the comparative efficacy and safety of B/FTC/TAF in treatment-experienced women. In terms of virologic failure, it was noted that the proportion of women experiencing virologic failure in Study 1961 (1.7% in both treatment groups) and was consistent with the proportion in Study 1878 (1.7% both treatment groups).

In particular, there may be harms, including potential impairment to renal, liver function, or bone density (all study patients were required to have adequate renal function: eGFR ≥ 50 mL/min [≥ 0.83 mL/s] according to the Cockcroft–Gault formula) for patients who do not meet these criteria. In the treatment-experienced/switch studies, patients were also

required to have hepatic transaminases (aspartate aminotransferase and alanine aminotransferase) ≤ 5 × upper limit of normal and total bilirubin ≤ 1.5 mg/dL (≤ 26 µmol/L), or normal direct bilirubin. Patients with other comorbidities, such as HBV, were excluded. It is unknown whether the drug could be used as effectively and safely in patients who were not included in the trials.

Efficacy

Only those efficacy outcomes identified in the CDR review protocol are reported in this section (Table 14 and Table 15).

FDA-defined snapshot algorithm: HIV-1 RNA < 50 copies/mL and HIV-1 RNA ≥ 50 copies/mL at 48 weeks

Treatment-Naive

In Study 1489 and 1490, the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 was the primary outcome (Table 14). In Study 1489, 92.4% of the B/FTC/TAF group and 93.0% of the ABC/DTG/3TC group had HIV-1 RNA < 50 copies/mL at week 48. The difference was –0.6% (95% CI, –4.8% to 3.6%, *P* = 0.78). The lower limit of the CI was above the a priori noninferiority margin of –12%, suggesting that B/FTC/TAF is noninferior to ABC/DTG/3TC. In Study 1490, 89.4% of the B/FTC/TAF group and 92.9% of the DTG + FTC/TAF group had HIV-1 RNA < 50 copies/mL at week 48. The difference was –3.5% (95% CI, –7.9% to 1.0%). The lower limit of the CI was above the a priori noninferiority margin of –12%, suggesting that B/FTC/TAF is noninferior to DTG + FTC/TAF.

In Study 1489, the proportion of patients in the per-protocol (PP) analysis set with HIV-1 RNA < 50 copies/mL at week 48 was consistent with the FAS and supported the conclusion of noninferiority of B/FTC/TAF to ABC/DTG/3TC (B/FTC/TAF: 99.3%; ABC/DTG/3TC: 98.6%; difference in proportion: 0.7%; 95% CI, −1.4% to 2.8%). In Study 1490, the proportion of subjects in the PP analysis set with HIV-1 RNA < 50 copies/mL at week 48 was consistent the FAS, supporting the conclusion of noninferiority of B/FTC/TAF to DTG+FTC/TAF (B/FTC/TAF: 98.9%; DTG + FTC/TAF: 99.7%; difference in percentages: −0.7%; 95% CI, −2.6% to 1.2%).

The proportion of patients with HIV-1 RNA ≥ 50 copies/mL was also identified as a key efficacy outcome in the review protocol (Table 4). In Study 1489, 1.0% of patients in the B/FTC/TAF group and 2.5% of patients in the ABC/DTG/3TC group had HIV-1 RNA ≥ 50 copies/mL at 48 weeks. The difference in proportions between groups and the corresponding 95% CI was not provided. In Study 1490, 4.4% of patients in the B/FTC/TAF group and 1.2% of patients in the DTG + FTC/TAF group had HIV-1 RNA ≥ 50 copies/mL at 48 weeks. The difference in proportions between groups and the corresponding 95% CI were not provided.

Treatment-Experienced

In Study 1844, Study 1878, and Study 1961, the proportion of patients with HIV-1 RNA ≥ 50 copies/mL was the primary outcome (Table 15). In Study 1844, 1.1% of the B/FTC/TAF group and 0.4% of the ABC/DTG/3TC group had HIV-1 RNA ≥ 50 copies/mL at week 48. The difference was 0.7% (95% CI, –1.0% to 2.8%). The upper limit of the CI did not exceed the a priori noninferiority margin of 4%, suggesting that B/FTC/TAF is noninferior to ABC/DTG/3TC. In Study 1878, 1.7% of the B/FTC/TAF group and 1.7% of the SBR group

(RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC) had HIV-1 RNA ≥ 50 copies/mL at week 48. The difference was 0.0% (95% CI, –2.5% to 2.5%, *P* value = 1.00). The upper limit of the CI did not exceed the a priori noninferiority margin of 4%, suggesting that B/FTC/TAF is noninferior to SBR. In Study 1961, 1.7% of the B/FTC/TAF group and 1.7% of the SBR group (E/C/FTC/TAF or E/C/FTC/TDF or ATV + RTV + FTC/TDF) had HIV-1 RNA ≥ 50 copies/mL at week 48. The difference was 0.0% (95% CI, –2.9% to 2.9%). The upper limit of the CI did not exceed the a priori noninferiority margin of 4%, suggesting that B/FTC/TAF is noninferior to SBR.

In Study 1844, 1878, and 1961, noninferiority was confirmed in the PP analysis set. In Study 1844, the percentages of subjects in the week 48 PP analysis set with HIV-1 RNA ≥ 50 copies/mL at week 48 were consistent with those for the FAS, supporting the conclusion of noninferiority of B/FTC/TAF to ABC/DTG/3TC (B/FTC/TAF 0.4%; ABC/DTG/3TC 0.0%; difference in percentages: 0.4%; 95% CI, −1.1% to 2.2%). In Study 1878, the percentages of subjects in the week 48 PP analysis set with HIV-1 RNA ≥ 50 copies/mL at week 48 were consistent with those for the FAS, supporting the conclusion of noninferiority of B/FTC/TAF to SBR (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC) (B/FTC/TAF 1.1%; SBR 0.8%; difference in percentages: 0.3%; 95% CI, −1.9% to 2.5%). In Study 1961, the percentages of subjects in the week 48 PP analysis set with HIV-1 RNA ≥ 50 copies/mL at week 48 was consistent with those for the FAS, supporting the conclusion of noninferiority of B/FTC/TAF to SBR (E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF) (B/FTC/TAF 1.8%; SBR 1.8%; difference in percentages 0.0%; 95.001% CI, −3.0% to 3.0%).

The proportion of patients with HIV-1 RNA < 50 copies/mL was also identified as a key efficacy outcome in the review protocol (Table 4). In Study 1844, 93.6% of the B/FTC/TAF group and 95.0% of the ABC/DTG/3TC group had HIV-1 RNA < 50 copies/mL at week 48. The difference in proportions between the groups was –1.4% (95% CI, –5.5% to 2.6%). In Study 1878, 92.1% of the B/FTC/TAF group and 88.9% of the SBR group (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC) had HIV-1 RNA < 50 copies/mL at week 48. The difference in proportions between the groups was 3.2% (95% CI, –1.6% to 8.2%). In Study 1961, 95.7% of the B/FTC/TAF and 95.3% of the SBR group (E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF) had HIV-1 RNA < 50 copies/mL at week 48. The difference in proportions between the groups was 0.4% (–3.7% to 4.5%).

Table 14: Virologic Outcome (Full Analysis Set): Treatment-Naive

Virologic Efficacy Outcomes n (%)	Study 1489		Study 1490	
	B/FTC/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/FTC/TAF (N = 320)	DTG + F/TAF (N = 325)
HIV-1 RNA < 50 Copies/mL				
Week 48, N (%)	290 (92.4)	293 (93.0)	286 (89.4)	302 (92.9)
P value	0.78		0.12	
Difference, % (95% CI)	–0.6 (–4.8 to 3.6)		–3.5 (–7.9 to 1.0)	
HIV-1 RNA ≥ 50 copies/mL				
Week 48, N (%)	3 (1.0)	8 (2.5)	14 (4.4)	4 (1.2)
P value	NR		NR	
Difference, % (95% CI)	NR		NR	
HIV-1 RNA ≥ 50 copies/mL in week 48 window, *N (%)*	2 (0.6)	6 (1.9)	3 (0.9)	1 (0.3)
Discontinued study drug due to lack of efficacy, *N (%)*	0	0	0	0

Virologic Efficacy Outcomes n (%)	Study 1489		Study 1490	
	B/FTC/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/FTC/TAF (N = 320)	DTG + F/TAF (N = 325)
Discontinued study drug due to other reasons[a] and last available HIV-1 RNA ≥ 50 copies/mL, *N (%)*	1 (0.3)	2 (0.6)	11 (3.4)	3 (0.9)
No virologic data in week 48 window, *N (%)*	21 (6.7)	14 (4.4)	20 (6.3)	19 (5.8)
Discontinued study drug due to AE/death, *N (%)*	0	4 (1.3)	3 (0.9)	3 (0.9)
Discontinued study drug due to other reasons[a] and last available HIV-1 RNA < 50 copies/mL, *N (%)*	16 (5.1)	9 (2.9)	11 (3.4)	14 (4.3)
Missing data during window but on study drug, *N (%)*	5 (1.6)	1 (0.3)	6 (1.9)	2 (0.6)
Missing = Failure at Week 48				
HIV-1 RNA < 50 copies / mL	290/314 (92.4)	294/315 (93.3)	288/320 (90.0)	304/325 (93.5))
Difference, % (95% CI)	–0.9 (–5.1 to 3.2)		–3.4 (–7.7 to 0.9)	
HIV-1 RNA ≥ 50 copies /mL	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)	NR		NR	
Missing = Excluded				
HIV-1 RNA < 50 copies / mL	290/292 (99.3)	294/301 (97.7)	288/291 (99.0)	304/306 (99.3)
Difference, % (95% CI)	1.6 (–0.7 to 4.0)		–0.4 (–2.3 to 1.6)	
HIV-1 RNA ≥ 50 copies /mL	[redacted]	[redacted]	[redacted]	[redacted]

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CI = confidence interval; DTG = dolutegravir; FTC/TAF = emtricitabine/tenofovir alafenamide; HIV-1 = HIV type 1; NR = not reported; RNA = ribonucleic acid.

[a] Other reasons include investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

Source: Clinical Study Report Study1489,[6] Clinical Study Report Study 1490.[7]

Table 15: Virologic Outcome (Full Analysis Set): Treatment-Experienced/Switch

Virologic Efficacy Outcomes n (%)	Study 1844		Study 1878		Study 1961	
	B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (N = 287)	B/FTC/TAF (N = 234)	SBR (N = 236)
HIV-1 RNA ≥ 50 Copies/mL						
Week 48, N (%)	3 (1.1)	1 (0.4)	5 (1.7)	5 (1.7)	4 (1.7)	4 (1.7)
P value	0.62		1.00		1.00	
Difference, % (95% CI)	0.7 (–1.0 to 2.8)		0.0 (–2.5 to 2.5)		0.0 (–2.9 to 2.9)	
HIV-1 RNA ≥ 50 copies/mL in week 48 window, *N (%)*	1 (0.4)	0	2 (0.7)	2 (0.7)	4 (1.7)	4 (1.7)
Discontinued study drug due to lack of efficacy, *N (%)*	0	0	1 (0.3)	0	0	0
Discontinued study drug due to AE/death and last available HIV-1 RNA ≥ 50 copies/mL, *N (%)*	1 (0.4)	0	0	0	0	0
Discontinued study drug due to other reasons[a] and last available HIV-1 RNA ≥ 50 copies/mL, *N (%)*	1 (0.4)	1 (0.4)	2 (0.7)	3 (1.0)	0	0
No virologic data in week 48 window, *N (%)*	15 (5.3)	13 (4.6)	18 (6.2)	27 (9.4)	6 (2.6)	7 (3.0)
Discontinued study drug due to AE/death, and last available HIV-1 RNA < 50 copies/mL, *N (%)*	5 (1.8)	2 (0.7)	3 (1.0)	2 (0.7)	0	1 (0.4)
Discontinued study drug due to other reasons[a] and last available HIV-1 RNA < 50 copies/mL, *N (%)*	5 (1.8)	9 (3.2)	10 (3.4)	19 (6.6)	3 (1.3)	4 (1.7)
Missing data during window but on study drug, *N (%)*	5 (1.8)	2 (0.7)	5 (1.7)	6 (2.1)	3 (1.3)	2 (0.8)
HIV-1 RNA < 50 Copies/mL						
Week 48, N (%)	264 (93.6)	267 (95.0)	267 (92.1)	255 (88.9)	224 (95.7)	225 (95.3)
P value	0.59		0.20		1.00	
Difference, % (95% CI)	–1.4 (–5.5 to 2.6)		3.2 (–1.6 to 8.2)		0.4 (–3.7 to 4.5)	
Missing = Failure at Week 48						
N	282	281	290	287	234	236
HIV-1 RNA < 50 copies / mL	268 (95.0)	268 (95.4)	269 (92.8)	261 (90.9)	225 (96.2)	225 (95.3)
Difference, % (95% CI)	–0.3 (–4.1 to 3.4)		1.8 (–2.8 to 6.5)		0.8 (–3.1 to 4.8)	
HIV 1 RNA ≥ 50 copies /mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing = Excluded						
N	269	268	272	264	229	229
HIV-1 RNA < 50 copies / mL	268 (99.6)	268 (100)	269 (98.9)	261 (98.9)	225 (98.3)	225 (98.3)
Difference, % (95% CI)	–0.4 (–2.1 to 1.1)		0.0 (–2.2 to 2.4)		0.0 (–2.9 to 2.9)	
HIV 1 RNA ≥ 50 copies /mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ABC/DTG/3TC = abacavir/dolutegravir /lamivudine; AE = adverse event; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CI = confidence interval; HIV-1 = HIV type 1; RNA = ribonucleic acid; SBR = stay on baseline regimen.

[a] Other reasons include investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

Source: Clinical Study Report Study 1844,[8] Clinical Study Report Study 1878,[9] Clinical Study Report Study 1961.[10]

Subgroup Analyses

Baseline Viral Load: Treatment-Naive

Study 1489 and Study 1490 identified baseline HIV-1 RNA (≤ 100,000 copies/mL and > 100,000 copies/mL) as a subgroup a priori (Table 16). However, subgroup-specific noninferiority margins were not defined, and therefore it is not possible to evaluate noninferiority in this context.

Table 16: HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 (Full Analysis Set): Treatment-Naive

	Study 1489		Study 1490	
	B/FTC/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/FTC/TAF (N = 320)	DTG + FTC/TAF (N = 325)
Baseline HIV-1 RNA (Copies/mL)				
≤ 100,000, n (%)	244/261 (93.5)	248/265 (93.6)	229/254 (90.2)	251/271 (92.6)
Difference %, 95% CI	[redacted]		[redacted]	
> 100,000, n (%)	46/53 (86.8)	45/50 (90.0)	57/66 (86.4)	51/54 (94.4)
Difference %, 95% CI	[redacted]		[redacted]	

ABC/DTG/3TC = abacavir/dolutegravir /lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CI = confidence interval; DTG = dolutegravir; FTC/TAF = emtricitabine/tenofovir alafenamide; HIV-1 = HIV type 1; NR = not reported; RNA = ribonucleic acid; SBR = stay on baseline regimen.

Source: Clinical Study Report Study1489,[6] Clinical Study Report Study 1490.[7]

Baseline Viral Load ≤ 100,000 Copies/mL

In Study 1489, more than 83% of patients, balanced across treatment groups, had HIV-1 RNA ≤ 100,000 copies/mL at baseline. At week 48, the proportion of patients with HIV-1 RNA < 50 copies/mL in the B/FTC/TAF group and in the ABC/DTG/3TC group was 93.5% and 93.6%, respectively (difference between groups[redacted]). In Study 1490, more than 80% of patients, balanced across treatment groups, had HIV-1 RNA had ≤ 100,000 copies/mL at baseline. At week 48, the proportion of patients with HIV-1 RNA < 50 copies/mL in the B/FTC/TAF group and in the DTG + FTC/TAF group was 90.2% and 92.6%, respectively (difference between groups: [redacted]).

Baseline Viral Load > 100,000 Copies/mL

In Study 1489, 16% of patients, balanced across treatment groups, had HIV-1 RNA > 100,000 copies/mL at baseline. The proportion of patients with HIV-1 RNA < 50 copies/mL in the B/FTC/TAF group and in the ABC/DTG/3TC group was 86.8% and 90.0%, respectively (difference between groups: [redacted]). In Study 1490, 21% of patients in the B/FTC/TAF group and 17% of patient in the DTG + FTC/TAF group had HIV-1 RNA > 100,000 copies/mL at baseline. At week 48, the proportion of patients with HIV-1 RNA < 50 copies/mL in the B/FTC/TAF group and in the DTG + FTC/TAF group was 86.4% and 94.4%, respectively (difference between groups: [redacted]).

Baseline ARV Regimens (Treatment-Experienced/Switch)

Eligibility criteria for Study 1844 included virologically suppressed HIV infection on a regimen of ABC (600 mg), DTG (50 mg), and 3TC (300 mg), in either a fixed-dose combination (FDC) or a multi-tablet regimen. Results were not stratified by FDC or multi-tablet regimen.

In Study 1878, patients had to have virologically suppressed HIV infection on a boosted PI regimen boosted ATV or DRV + either FTC and TDF or ABC and 3TC. Results were not presented by the four possible baseline regimens.

In Study 1961, patients who participated in four predefined studies by the manufacturer were eligible to participate. Eligible patients had to have virologically suppressed HIV infection on a regimen of E/C/FTC/TAF, E/C/FTC/TDF, or ATV + RTV + FTC/TDF. Results were not presented stratified by baseline regimen.

Other Efficacy Outcomes

Resistance

Treatment-Naive

In Study 1489 and 1490, no patients developed treatment-emergent resistance to any study drug up to the data cut date.

Treatment-Experienced/Switch

In Study 1844, no patients developed treatment-emergent resistance to any study drug. In Study 1878, no patients in the B/FTC/TAF group developed treatment-emergent drug resistance. One patient in the SBR group (on a regimen of RTV-boosted DRV + ABC/3TC) developed L74V in reverse transcriptase.

In Study 1961, although genotypic analysis of protease, reverse transcriptase, and integrase was not conducted at screening, genotypic data for at least one gene was available at baseline for all 470 subjects in the FAS. Genotypic analysis was conducted in the manufacturer's studies in which these women were previously enrolled. HIV-1 genotypes with protease and reverse transcriptase data were available for 470 of 470 (100%) subjects in the FAS. HIV-1 genotypes with integrase data were available for 276 of 470 (58.7%) subjects in the FAS. Primary INSTI resistance at baseline was document in three patients (2.1%) in the B/FTC/TAF group and five patients (3.7%) in the SBR group. Primary NRTI resistance at baseline was document in five patients (2.1%) in the B/FTC/TAF group and six patients (2.5%) in the SBR group. Overall, the prevalence of baseline resistance-associated mutations was similar between treatment groups (Table 27).

One subject in the B/FTC/TAF group was included in the resistance analysis population and evaluated for the development of resistance through week 48. For this subject, no resistance mutations emerged (Table 23) and the HIV-1 RNA resuppressed to < 50 copies/mL with further B/FTC/TAF treatment. Two subjects in the SBR group, both taking E/C/FTC/TAF, were included in the resistance analysis population and evaluated for the development of resistance through week 48. One subject developed M184M/I/V at week 48 (Table 23). This subject switched to B/FTC/TAF in the extension portion of the study and subsequently showed resuppression of the virus (HIV-1 RNA < 50 copies/mL). The other subject had no emergent resistance and did not resuppress HIV-1 RNA to < 50 copies/mL through week 48.

Health-Related Quality of Life

Treatment-Naive

The SF-36 was used to measure HRQoL in both Study 1489 and Study 1490. Although SF-36 data were requested for both Study 1489 and Study 1490, the manufacturer provided

results for Study 1489 only[31] (data presented in Table 17). The SF-36 scores were presented as SF-36 PCS and SF-36 MCS. The change from baseline for both the PCS and MCS appear similar between groups. However, the number of patients contributing data at 48 weeks was unclear, as was the method to account for missing data, and there was no control of type I error. These data should be considered exploratory.

Treatment-Experienced/Switch

The SF-36 was measured in Study 1844 and 1878. HRQoL was not measured in Study 1961. Although SF-36 data were requested for Study 1844 and Study 1878, the manufacturer-provided results for Study 1844 only[31] (data presented in Table 18). The SF-36 scores are presented as SF-36 PCS and SF-36 MCS. Interpretation of these data are similarly limited by the unknown methods to account for any missing data and lack of control of type I error; they should be considered exploratory.

Table 17: Other Efficacy Outcomes — Health-Related Quality of Life: Treatment-Naive

Quality of Life	Study 1489		Study 1490	
	B/FTC/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/FTC/TAF (N = 320)	DTG + FTC/TAF (N = 325)
SF-36 PCS[a]				
Baseline	57.4 (52.6 to 60.0)	56.6 (52.2 to 59.3)	NP	NP
48 weeks	NR	NR	NP	NP
Median change, IQR	0.1 (–3.3 to 3.1)	0.2 (–2.6 to 2.8)	NP	NP
P value, median change	0.85			
SF-36 MCS[a]				
Baseline	49.0 (37.7 to 55.2)	49.5 (40.0 to 56.3)	NP	NP
48 weeks	NR	NR	NP	NP
Median change, IQR	2.3 (–1.6 to 9.0)	2.1 (–4.0 to 7.0)	NP	NP
P value, median change	0.090			

ABC/DTG/3TC = abacavir/dolutegravir /lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; FTC/TAF = emtricitabine/tenofovir alafenamide; IQR = interquartile range; MCS = mental component summary; NP = not provided by manufacturer; NR = not reported; PCS = physical component summary; SD = standard deviation.

[a] SF-36 PCS and MCS scores are normally distributed with a mean of 50 and a standard deviation of 10, with higher scores indicating better health.

Source: Wohl et al.[31]

Table 18: Other Efficacy Outcomes — Health-Related Quality of Life: Treatment-Experienced/Switch

Quality of Life	Study 1844		Study 1878		Study 1961	
	B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (N = 287)	B/FTC/TAF (N = 234)	SBR (N = 236)
SF-36 PCS[a]						
Baseline	55.5 (50.5, 59.1)	56.6 (51.0, 59.2)	NP	NP	NA	NA
48 weeks	NR	NR	NP	NP	NA	NA
Median change, IQR	–0.4 (–3.6 to 2.7)	0.2 (–2.3 to 2.7)	NP	NP	NA	NA
P value, median change	0.17					
SF-36 MCS[a]						
Baseline	51.9 (44.5 to 57.5)	53.2 (46.6 to 57.6)	NP	NP	NA	NA

Quality of Life	Study 1844		Study 1878		Study 1961	
	B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (N = 287)	B/FTC/TAF (N = 234)	SBR (N = 236)
48 weeks	NR	NR	NP	NP	NA	NA
Median change, IQR	0.3 (–3.0 to 4.6)	0.1 (–3.9 to 3.5)	NP	NP	NA	NA
P value, median change	0.13					

ABC/DTG/3TC = abacavir/dolutegravir /lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; IQR = interquartile range; MCS = mental component summary; NA = not applicable; NP = not provided by manufacturer; NR = not reported; PCS= physical component summary; SBR = stay on baseline regimen; SD = standard deviation.

[a] SF-36PCS and MCS scores are normally distributed with a mean of 50 and a standard deviation of 10, with higher scores indicating better health.

Source: Wohl et al.[31]

Adherence

Treatment-Naive

In Study 1489 and Study 1490, the safety analysis set was used to report adherence to week 48 (Table 19). Adherence for both studies was calculated based on pill count for the active drugs only. In Study 1489, mean adherence (SD) was [redacted] and [redacted] in the B/FTC/TAF group and in the ABC/DTG/3TC group, respectively. However, the proportion of patients reporting 95% or higher adherence was numerically higher in the B/FTC/TAF group ([redacted]) compared with the ABC/DTG/3TC group ([redacted]). In Study 1490, mean adherence was [redacted] and [redacted] in the B/FTC/TAF group and in the DTG+FTC/TAF group, respectively. The proportion of patients reporting 95% or higher adherence was [redacted] in the B/FTC/TAF group and the [redacted] in the DTG + FTC/TAF group.

Treatment-Experienced/Switch

In Study 1844, 1878, and 1961, the safety analysis set was used to report adherence to week 48 (Table 20). Adherence for these three studies was calculated based on pill count for the active drugs only. In Study 1844, mean adherence was [redacted] and [redacted] in the B/FTC/TAF and ABC/DTG/3TC groups, respectively. The proportion of patients reporting 95% or higher adherence was [redacted] in the B/FTC/TAF group and [redacted] in the ABC/DTG/3TC group. In Study 1878, adherence was reported for the B/FTC/TAF group only. Mean adherence in the B/FTC/TAF group was [redacted] and [redacted] reported 95% or higher adherence. In Study 1961, mean adherence was [redacted] and [redacted] in the B/FTC/TAF and SBR (E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF) groups, respectively. The proportion of patients reporting 95% or higher adherence was [redacted] (B/FTC/TAF) and [redacted] (SBR: E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF).

Table 19: Other Efficacy Outcomes — Adherence to Study Drugs Up to Week 48 Visit (Safety Analysis Set): Treatment-Naive

Adherence	Study 1489		Study 1490	
	B/FTC/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/FTC/TAF (N = 320)	DTG + FTC/TAF (N = 325)
Patients with calculable adherence,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adherence Rate up to Week 48				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Adherence	Study 1489		Study 1490	
	B/FTC/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/FTC/TAF (N = 320)	DTG + FTC/TAF (N = 325)
Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]
< 80%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 80% to < 90%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 90% to < 95%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 95%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

ABC/DTG/3TC = abacavir/dolutegravir /lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; FTC/TAF = emtricitabine/tenofovir alafenamide; IQR = interquartile range; NR = not reported; SD = standard deviation.

[redacted]

Source: Clinical Study Report Study1489,[6] Clinical Study Report Study 1490.[7]

Table 20: Other Efficacy Outcomes — Adherence to Study Drugs Up to Week 48 Visit (Safety Analysis Set): Treatment-Experienced/Switch

Adherence	Study 1844		Study 1878		Study 1961	
	B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (N = 287)	B/FTC/TAF (N = 234)	SBR (N = 236)
Patients with calculable adherence,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adherence Rate up to Week 48						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
< 80%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 80% to < 90%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 90% to < 95%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 95%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ABC/DTG/3TC = abacavir/dolutegravir /lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; IQR = interquartile range; NR = not reported; SBR = stay on baseline regimen; SD = standard deviation.

[redacted]

Source: Clinical Study Report Study 1844,[8] Clinical Study Report Study 1878,[9] Clinical Study Report Study 1961.[10]

Harms

Only those harms identified in the review protocol are reported in this section (Table 4).

Treatment-Naive

Adverse Events

In Study 1489, 84.4% and 89.8% of patients in the B/FTC/TAF and ABC/DTG/3TC groups, respectively, experienced at least one AE (Table 21). In Study 1490, 82.5% and 83.7% of patients in the B/FTC/TAF and DTG + FTC/TAF groups experienced at least one AE. The most common AEs across studies (> 10%) were diarrhea, headache, and nausea.

Serious Adverse Events

In Study 1489, a similar proportion of patients reported at least one SAE (B/FTC/TAF: 6.1%, ABC/DTG/3TC: 7.9%). In Study 1490, a numerically higher proportion of patients in the B/FTC/TAF group reported at least one SAE (12.2%) compared with the DTG + FTC/TAF group (7.1%) (Table 21). No single SAE occurred in more than 1% of patients.

There were no deaths in Study 1489. There were three deaths in Study 1490 (B/FTC/TAF: one due to cardiac arrest following appendicitis and septic shock; DTG + FTC/TAF: one from unknown causes, one due to pulmonary embolism). None of the deaths were deemed related to treatment.

Withdrawals Due to Adverse Events

In Study 1489, there were no withdrawals due to adverse events (WDAEs) in the B/FTC/TAF group, and there were 4 (1.3%) WDAEs in the ABC/DTG/3TC group. In Study 1490, there were five (1.6%) WDAEs in the B/FTC/TAF group and one (0.3%) WDAE in the DTG + FTC/TAF group.

Notable Harms

Several notable harms were identified by the review team, including the clinical expert consulted for this review. No specific harms were identified by input received from patient groups (Appendix 1: Patient Input Summary). Notable harms included renal- and bone-related harms as well as anxiety, depression, insomnia, headache, diarrhea, nausea, and vomiting.

Renal-Related

In Study 1489, mean serum creatinine was similar at baseline between treatment groups (B/FTC/TAF: 0.92 mg/dL, SD 0.28, ABC/DTG/3TC: 0.92 mg/dL, SD 0.17). Both treatment groups experienced an increase in serum creatinine from baseline to week 48 (mean change B/FTC/TAF: [redacted]), ABC/DTG/3TC: [redacted]). In Study 1490, mean serum creatinine was similar at baseline between treatment groups (B/FTC/TAF: 0.93 mg/dL, SD 0.22 mg/dL; DTG + FTC/TAF: 0.89 mg/dL, SD 0.12 mg/dL). Both treatment groups experienced an increase in serum creatinine from baseline to week 48 (mean change B/FTC/TAF: [redacted], DTG + FTC/TAF: [redacted]).

In Study 1489, mean eGFR was similar at baseline between treatment groups (B/FTC/TAF: 131.0 mL/min/1.73 m^2, SD 39.4), ABC/DTG/3TC: 128.8 mL/min/1.73 m^2, SD 33.3 mL/min/1.73 m^2). Both treatment groups experienced a decline in eGFR from baseline to week 48 (mean change B/FTC/TAF: [redacted], ABC/DTG/3TC: [redacted]). In Study 1490, mean eGFR was similar at baseline between treatment groups (B/FTC/TAF: 122.8 mL/min/1.73 m^2, SD 31.6 mL/min/1.73 m^2; DTG + FTC/TAF: 129.2 mL/min/1.73 m^2, SD 40.6 mL/min/1.73 m^2). Both treatment groups experienced a decline in eGFR from baseline to week 48 (mean change B/FTC/TAF: [redacted], ABC/DTG/3TC: [redacted]).

Bone-Related

BMD was measured in Study 1489 but not in Study 1490. In Study 1489, BMD was measured at the hip and at the spine. Mean hip BMD was similar at baseline between treatment groups (B/FTC/TAF: 1.048 g/cm^2, SD 0.157; ABC/DTG/3TC: 1.057 g/cm^2, SD

0.152). Both treatment groups experienced a decline in hip BMD from baseline to week 48 (mean change B/FTC/TAF: –0.783%, SD 2.22%; ABC/DTG/3TC: –1.021%, SD 2.31%).

Mean spine BMD was similar at baseline between treatment groups (B/FTC/TAF: 1.138 g/cm^2, SD 0.184; ABC/DTG/3TC: 1.142 g/cm^2, SD 0.171). Both treatment groups experienced a decline in spine BMD from baseline to week 48 (mean change B/FTC/TAF: –0.831%, SD 3.19%; ABC/DTG/3TC: –0.596%, SD 3.10%).

Anxiety

In Study 1489, 0.3% and 1.0% of patients reported anxiety in the B/FTC/TAF group and the ABC/DTG/3TC group, respectively. In Study 1490, 0.6% and 4.6% of patients reported anxiety in the B/FTC/TAF and DTG + FTC/TAF groups, respectively.

Depression

In Study 1489, 0% and 0.6% of patients reported depression in the B/FTC/TAF group and the ABC/DTG/3TC group, respectively. In Study 1490, 3.4% of patients in both treatment groups reported depression.

Insomnia

In Study 1489, 4.5% and 6.3% of patients reported insomnia in the B/FTC/TAF and ABC/DTG/3TC groups, respectively. In Study 1490, 5.0% and 4.3% of patients reported insomnia in the B/FTC/TAF group and DTG + FTC/TAF group, respectively.

Headache

In Study 1489, 11.5% and 13.7% of patients reported headache in the B/FTC/TAF group and the ABC/DTG/3TC group, respectively. In Study 1490, 12.5% and 13.3% of patients reported headache in the B/FTC/TAF group and the DTG + FTC/TAF group, respectively.

Diarrhea

In Study 1489, 12.7% and 13.0% of patients reported diarrhea in the B/FTC/TAF group and the ABC/DTG/3TC group, respectively. In Study 1490, 11.6% and 12.0% of patients reported diarrhea in the B/FTC/TAF group and the DTG + FTC/TAF group, respectively.

Nausea

In Study 1489, 10.2% and 22.9% of patients reported nausea in the B/FTC/TAF group and the ABC/DTG/3TC group, respectively. In Study 1490, 7.8% and 8.9% of patients reported nausea in the B/FTC/TAF group and the DTG + FTC/TAF group, respectively.

Vomiting

In Study 1489, 3.8% and 5.4% of patients reported vomiting in the B/FTC/TAF group and the ABC/DTG/3TC group, respectively. In Study 1490, 4.4% and 3.1% of patients reported vomiting in the B/FTC/TAF group and the DTG + FTC/TAF group, respectively.

Treatment-Experienced/Switch

Adverse Events

In Study 1844 and Study 1878, more than 78% of patients experienced at least one AE (Table 22), and the proportion of patients experiencing an AE was balanced across study groups in both trials. In Study 1961, a numerically smaller proportion of patients experienced at least one AE compared with Study 1844 and Study 1878 (B/FTC/TAF: 65.8%; SBR: 67.4%) (Table 22). The most common AEs were upper respiratory tract infection, nasopharyngitis, and headache.

Serious Adverse Events

In Study 1844, 5.3% and 7.8% of patients experienced at least one serious adverse event (SAE) in the B/FTC/TAF group and the ABC/DTG/3TC group, respectively. In Study 1878, 5.9% and 7.0% of patients experienced at least one SAE in the B/FTC/TAF group and the SBR group (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC), respectively. In Study 1961, 3.0% and 3.4% of patients experienced at least one SAE in the B/FTC/TAF group and the SBR (E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF) group, respectively. No single SAE occurred in more than 1% of patients.

There were two deaths in Study 1844, both in the B/FTC/TAF group (one cardiac death as a result of hypertensive and atherosclerotic cardiovascular disease and one due to unknown cause). There were two deaths in Study 1878 (in the B/FTC/TAF group, one due to complications from lung cancer; in the SBR group [RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC], one due to blunt force trauma to the head). In Study 1961, there was one death (in the SBR group [E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF], one due to influenza). None of the deaths were deemed related to treatment.

Withdrawals Due to Adverse Events

In Study 1844, 2.1% and 0.7% of patients withdrew due to AEs in the B/FTC/TAF group and the ABC/DTG/3TC groups, respectively. In Study 1878, 0.7% and 0.3% of patients withdrew due to AEs in the B/FTC/TAF group and in the SBR group (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC), respectively. In Study 1961, no patients withdrew due to an AE.

Notable Harms

Several notable harms were identified by the review team, including the clinical expert consulted for this review. No harms were identified through input received from patient groups (Appendix 1: Patient Input Summary). Notable harms included renal- and bone-related harms as well as anxiety, depression, insomnia, headache, diarrhea, nausea, and vomiting.

Renal-Related

In Study 1844, mean serum creatinine was similar at baseline between treatment groups (B/FTC/TAF: 1.06 mg/dL; standard deviation [SD] 0.196 mg/dL), ABC/DTG/3TC: 1.06 mg/dL; SD 0.179 mg/dL). Both treatment groups experienced negligible changes in serum creatinine from baseline to week 48 (mean change B/FTC/TAF: [redacted], ABC/DTG/3TC: [redacted]). In Study 1878, mean serum creatinine was similar at baseline between treatment groups (B/FTC/TAF: 0.98 mg/dL; SD 0.213 mg/dL; SBR [RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC]: 0.98 mg/dL, SD 0.183 mg/dL). The change in mean serum creatinine from baseline to week 48 was [redacted] and [redacted] in the B/FTC/TAF group and the SBR group (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC), respectively. In Study 1961, mean serum creatinine was similar at baseline between treatment groups (B/FTC/TAF: 0.81 mg/dL, SD 0.137 mg/dL; SBR 0.79 mg/dL, SD 0.139 mg/dL). The change in mean serum creatinine from baseline to week 48 was [redacted] and [redacted] in the B/FTC/TAF group and the SBR group (E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF), respectively.

In Study 1844, mean eGFR was similar at baseline between treatment groups (B/FTC/TAF: 104.3 mL/min, SD 32.16 mL/min; ABC/DTG/3TC: 104.9 mL/min, SD 30.78 mL/min). The change in mean eGFR from baseline to week 48 was [redacted] and [redacted] in the B/FTC/TAF group and the ABC/DTG/3TC, respectively. In Study 1878, mean eGFR was similar at baseline between treatment groups (B/FTC/TAF: 109.9 mL/min, SD 30.97 mL/min; SBR [RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC]: 108.4 mL/min, SD 31.75 mL/min). The change in mean eGFR from baseline to week 48 was [redacted] and [redacted] in the B/FTC/TAF group and the SBR (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC) group, respectively. In Study 1961, mean eGFR at baseline was 103.0 mL/min and 107.7 mL/min in the B/FTC/TAF group and the SBR (E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF) group, respectively. Both treatment groups experienced a decline in eGFR from baseline to week 48 (B/FTC/TAF: [redacted], SBR: [redacted]).

Bone-Related

BMD was measured in Study 1844 but was not measured in Study 1878 and Study 1961. In Study 1844, BMD was measured at the hip and at the spine. Mean hip BMD was similar at baseline between treatment groups (B/FTC/TAF: 1.006 g/cm^2, SD 0.147; ABC/DTG/3TC: 0.996 g/cm^2, SD 0.136). Both treatment groups experienced an increase in hip BMD from baseline to week 48 (mean change B/FTC/TAF: 0.156%, SD 2.21%; ABC/DTG/3TC: 0.299%, SD 2.11%).

Mean spine BMD was similar at baseline between treatment groups (B/FTC/TAF: 1.124 g/cm^2, SD 0.183; ABC/DTG/3TC: 1.103 g/cm^2, SD 0.155). Both treatment groups experienced an increase in spine BMD from baseline to week 48 (mean change B/FTC/TAF: 0.692%, SD 3.13%; ABC/DTG/3TC: 0.416%, SD 2.99%).

Anxiety

In Study 1844, 0.7% and 1.4% of patients reported anxiety in the B/FTC/TAF and ABC/DTG/3TC groups, respectively. In Study 1878, 3.4% and 1.7% of patients reported anxiety in the B/FTC/TAF and SBR (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC) groups, respectively. In Study 1961, 0.9% and 0% of patients reported anxiety in the B/FTC/TAF and SBR (E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF) groups, respectively.

Depression

In Study 1844, 1.1% and 3.6% of patients reported depression in the B/FTC/TAF and ABC/DTG/3TC groups, respectively. In Study 1878, 1.4% and 1.4% of patients reported depression in the B/FTC/TAF and SBR (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC) groups, respectively. In Study 1961, 0% and 0.4% of patients reported depression in the B/FTC/TAF and SBR (E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF) groups, respectively.

Insomnia

Across all three studies, insomnia was reported in 5% or fewer of patients. In Study 1844, 2.8% and 5.0% of patients reported insomnia in the B/FTC/TAF group and ABC/DTG/3TC group, respectively. In Study 1878, 3.4% and 2.1% of patients reported insomnia in the B/FTC/TAF group and SBR groups, respectively. In Study 1961, 2.7% and 0% of patients reported insomnia in the B/FTC/TAF group and the SBR group, respectively.

Headache

In Study 1844, 6.7% and 7.5% of patients experienced headache in the B/FTC/TAF and ABC/DTG/3TC group, respectively. In Study 1878, 12.1% and 4.2% of patients experienced headache in the B/FTC/TAF and SBR (RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC) groups, respectively. In Study 1961, 5.6% and 5.5% of patients experienced headache in the B/FTC/TAF and SBR (E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF) groups, respectively.

Diarrhea

In Study 1844, 8.5% and 5.0% of patients reported diarrhea in the B/FTC/TAF group and the ABC/DTG/3TC group, respectively. In Study 1878, 8.3% and 6.3% of patients reported diarrhea in the B/FTC/TAF group and the SBR group, respectively. In Study 1961, 2.6% and 1.3% of patients reported diarrhea in the B/FTC/TAF group and in the SBR group, respectively.

Nausea

Across all three studies, nausea was reported in fewer than 5% of patients. In Study 1844, 1.4% and 4.3% of patients reported nausea in the B/FTC/TAF group and the ABC/DTG/3TC group, respectively. In Study 1878, 3.8% and 1.7% of patients reported nausea in the B/FTC/TAF group and the SBR group, respectively. In Study 1961, 2.1% and 0.4% of patients reported nausea in the B/FTC/TAF group and the SBR group, respectively.

Vomiting

Across all three studies, vomiting was reported in fewer than 3% of patients. In Study 1844, 2.5% and 1.4% of patients reported vomiting in the B/FTC/TAF group and the ABC/DTG/3TC group, respectively. In Study 1878, 2.8% and 1.0% of patients reported vomiting in the

B/FTC/TAF group and the SBR group, respectively. In Study 1961, 1.7% and 0.4% of patients reported vomiting in the B/FTC/TAF group and the SBR group, respectively.

Table 21: Harms (Safety Analysis Set): Treatment-Naive

	Study 1489		Study 1490	
	B/FTC/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/FTC/TAF (N = 320)	DTG + FTC/TAF (N = 325)
AEs				
Patients with > 0 AE, n (%)	265 (84.4)	283 (89.8)	264 (82.5)	272 (83.7)
Most common AEs[a]				
Diarrhea	40 (12.7)	41 (13.0)	37 (11.6)	39 (12.0)
Headache	36 (11.5)	43 (13.7)	40 (12.5)	40 (12.3)
Nausea	32 (10.2)	72 (22.9)	25 (7.8)	29 (8.9)
Nasopharyngitis	23 (7.3)	29 (9.2)	22 (6.9)	31 (9.5)
Upper respiratory tract infection	20 (6.4)	34 (10.8)	15 (4.7)	23 (7.1)
Cough	20 (6.4)	8 (2.5)	11 (3.4)	16 (4.9)
Fatigue	19 (6.1)	27 (8.6)	19 (5.9)	26 (8.0)
Insomnia	14 (4.5)	20 (6.3)	16 (5.0)	14 (4.3)
Syphilis	12 (3.8)	25 (7.9)	11 (3.4)	12 (3.7)
Vomiting	12 (3.8)	17 (5.4)	14 (4.4)	10 (3.1)
Arthralgia	11 (3.5)	19 (6.0)	16 (5.0)	9 (2.8)
Bronchitis	10 (3.2)	16 (5.1)	5 (1.6)	13 (4.0)
Abdominal pain	9 (2.9)	16 (5.1)	12 (3.8)	6 (1.8)
Pyrexia	[redacted]	[redacted]	14 (4.4)	21 (6.5)
Back pain	[redacted]	[redacted]	11 (3.4)	20 (6.2)
Lymphadenopathy	[redacted]	[redacted]	17 (5.3)	18 (5.5)
Influenza	[redacted]	[redacted]	17 (5.3)	10 (3.1)
SAEs				
Patients with > 0 SAEs, N (%)	19 (6.1)	25 (7.9)	39 (12.2)	23 (7.1)
Most common SAEs[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]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs				
WDAEs, N (%)	0	4 (1.3)	5 (1.6)	1 (0.3)
Deaths				
Number of deaths, N (%)	0	0	1 (0.3)	2 (0.6)
Notable Harms				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Study 1489		Study 1490	
		B/FTC/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/FTC/TAF (N = 320)	DTG + FTC/TAF (N = 325)
Insomnia		14 (4.5)	20 (6.3)	16 (5.0)	14 (4.3)
Headache		36 (11.5)	43 (13.7)	40 (12.5)	40 (12.3)
Diarrhea		40 (12.7)	41 (13.0)	37 (11.6)	39 (12.0)
Nausea		32 (10.2)	72 (22.9)	25 (7.8)	29 (8.9)
Vomiting		12 (3.8)	17 (5.4)	14 (4.4)	10 (3.1)
Renal-Related:					
Serum Creatinine (mg/dL)					
Baseline	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	P value	[redacted]		[redacted]	
Change from baseline at week 48	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	P value	[redacted]		[redacted]	
$eGFR_{CG}$ (mL/min/1.73 m^2)					
Baseline	N	314	315	320	325
	Mean (SD)	131.0 (39.44)	128.8 (33.32)	122.8 (31.59)	129.2 (40.57)
	P value	[redacted]		[redacted]	
Change from baseline to week 48	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	P value	[redacted]		[redacted]	
Bone-Related:					
Hip BMD					
Baseline (g/cm^2)	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in LSM (95% CI)	[redacted]		[redacted]	
	P value	[redacted]		[redacted]	
% change at week 48	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in LSM (95% CI)	[redacted]		[redacted]	
	P value	[redacted]		[redacted]	
Spine BMD					
Baseline (g/cm^2)	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in LSM (95% CI)	[redacted]		[redacted]	
	P value	[redacted]		[redacted]	
% change at week 48	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in LSM (95% CI)	[redacted]		[redacted]	
	P value	[redacted]		[redacted]	

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; AE = adverse event; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BMD = bone mineral density; DTG = dolutegravir; FTC/TAF = emtricitabine/tenofovir alafenamide; CI = confidence interval; $eGFR_{CG}$ = estimated glomerular filtration rate (Cockcroft–Gault); LSM = least squares mean; NR = not reported; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] Frequency greater than 5% in at least one treatment arm across included studies.

Source: Clinical Study Report Study1489,[6] Clinical Study Report Study 1490.[7]

Table 22: Harms: Treatment-Experienced/Switch

		Study 1844		Study 1878		Study 1961	
		B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (N = 287)	B/FTC/TAF (N = 234)	SBR (N = 236)
AEs							
Patients with > 0 AEs, n (%)		225 (79.8)	225 (80.1)	233 (80.3)	226 (78.7)	154 (65.8)	159 (67.4)
Most common AEs[a]							
Upper respiratory tract infection		29 (10.3)	27 (9.6)	21 (7.2)	22 (7.7)	15 (6.4)	14 (5.9)
Nasopharyngitis		20 (7.1)	22 (7.8)	21 (7.2)	34 (11.8)	18 (7.7)	15 (6.4)
Headache		19 (6.7)	21 (7.5)	35 (12.1)	12 (4.2)	13 (5.6)	13 (5.5)
Diarrhea		24 (8.5)	14 (5.0)	24 (8.3)	18 (6.3)	6 (2.6)	3 (1.3)
Arthralgia		19 (6.7)	10 (3.6)	12 (4.1)	15 (5.2)	9 (3.8)	7 (3.0)
Insomnia		8 (2.8)	14 (5.0)	10 (3.4)	6 (2.1)	4 (1.7)	0
Back pain		10 (3.5)	7 (2.5)	13 (4.5)	17 (5.9)	8 (3.4)	8 (3.4)
[redacted]							
[redacted]							
SAEs							
Patients with > 0 SAEs, N (%)		15 (5.3)	22 (7.8)	17 (5.9)	20 (7.0)	7 (3.0)	8 (3.4)
Most common SAEs[a]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
WDAEs							
WDAEs, N (%)		6 (2.1)	2 (0.7)	2 (0.7)	1 (0.3)	0	0
Deaths							
Number of deaths, N (%)		2 (0.7)	0	1 (0.3)	1 (0/3)	0	1 (0.4)
Notable Harms							
[redacted]							
[redacted]							
Insomnia		8 (2.8)	14 (5.0)	10 (3.4)	6 (2.1)	4 (1.7)	0
Headache		19 (6.7)	21 (7.5)	35 (12.1)	12 (4.2)	13 (5.6)	13 (5.5)
Diarrhea		24 (8.5)	14 (5.0)	24 (8.3)	18 (6.3)	6 (2.6)	3 (1.3)
Nausea		4 (1.4)	12 (4.3)	11 (3.8)	5 (1.7)	5 (2.1)	1 (0.4)
Vomiting		7 (2.5)	4 (1.4)	8 (2.8)	3 (1.0)	4 (1.7)	1 (0.4)
Renal-Related:							
Serum Creatinine (mg/dL)							
Baseline	N						
	Mean (SD)						
Change from baseline at week 48	N						
	Mean (SD)						
	P value						
$eGFR_{CG}$ (mL/min/1.73 m^2)							

		Study 1844		Study 1878		Study 1961	
		B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (N = 287)	B/FTC/TAF (N = 234)	SBR (N = 236)
Baseline	N	282	281	290	287	[redacted]	[redacted]
	Mean (SD)	104.3 (32.16)	104.9 (30.78)	109.9 (30.97)	108.4 (31.75)	[redacted]	[redacted]
Change from baseline to week 48	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	P value	[redacted]		[redacted]		[redacted]	
Bone-Related:							
Hip BMD							
Baseline (g/cm^2)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in LSM (95% CI)	[redacted]		[redacted]		[redacted]	
% change at week 48	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in LSM (95% CI)	[redacted]		[redacted]		[redacted]	
	P value	[redacted]		[redacted]		[redacted]	
Spine BMD							
Baseline (g/cm^2)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in LSM (95% CI)	[redacted]		[redacted]		[redacted]	
% change at week 48	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in LSM (95% CI)	[redacted]		[redacted]		[redacted]	
	P value	[redacted]		[redacted]		[redacted]	

ABC/DTG/3TC = abacavir/dolutegravir /lamivudine; AE = adverse event; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BMD = bone mineral density; CI = confidence interval; $eGFR_{CG}$ = estimated glomerular filtration rate (Cockcroft–Gault); LSM = least squares mean; NR = not reported; SAE = serious adverse event; SBR = staying on baseline regimen; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] Frequency greater than 5% in at least one treatment arm across included studies.

Source: Clinical Study Report Study 1844,[8] Clinical Study Report Study 1878,[9] Clinical Study Report Study 1961.[10]

Discussion

Summary of Available Evidence

Two studies (Study 1489, Study 1490) were undertaken in treatment-naive adults. Both studies were randomized, double-blind, double-dummy, noninferiority trials. The primary outcome for both studies was virologic suppression, defined as the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 (calculated using the FDA-defined snapshot algorithm). The noninferiority margin was –12% and is consistent with the FDA recommendation for the outcome of interest. The comparators are all available in Canada and used in current clinical practice: ABC/DTG/3TC (Study 1489) and DTG + FTC/TAF (Study 1490). In the DHHS guidelines, these are listed as "recommended initial regimens for most people with HIV."[4]

Three studies (Study 1844, Study 1878, and Study 1961) were undertaken in treatment-experienced/switch populations with virologic suppression of HIV-1 on their current regimen. Study 1961 was conducted in women only. Study 1844 was a randomized, double-blind, double-dummy, noninferiority study. Study 1878 and Study 1961 were randomized, open-label, noninferiority studies. The primary outcome for the three studies was virologic failure, defined as the proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48 (calculated using the FDA-defined snapshot algorithm). The noninferiority margin was 4% and is consistent with the FDA recommendation for assessing virologic failure. The comparators are all available in Canada: ABC/DTG/3TC (Study 1844); RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC (Study 1878); and E/C/FTC/TAF or E/C/FTC/TDF or ATV + RTV + FTC/TDF (Study 1961). In the DHHS guidelines concerning "regimen switching in the settling of virologic suppression," the guidelines indicate that the "fundamental principle of regimen switching is to maintain viral suppression without jeopardizing future treatment options," and recommendations are specific to the patient's ARV treatment history.[4] However, according to the clinical expert consulted for this review, the comparators in Study 1878 are no longer frequently used regimens in Canadian practice. Given the inclusion criteria in the trials enrolling treatment-experienced patients (HIV-1 RNA < 50 copies/mL at screening), the included trials provide no evidence for the use of B/FTC/TAF in adults who have failed prior treatment.

Interpretation of Results

Efficacy

The design features of the five trials included in this review (e.g., blinding, allocation concealment) minimize the risk of selection bias, performance bias, detection bias, and attrition bias. The primary outcome for all trials was consistent with the FDA-defined snapshot algorithm: in trials of treatment-naive patients, virologic success (HIV-1 RNA < 50 copies/mL at week 48), and in trials of treatment-experienced/switch patients, virologic failure (HIV-1 RNA ≥ 50 copies/mL at week 48). All trials met the a priori defined noninferiority margin: –12% for treatment-naive and 4% for treatment-experienced/switch patients. The studies are ongoing, and week 48 data were provided by the manufacturer. The durability of response will require evaluation when long-term data are available for these trials.

Treatment-Naive

In treatment-naive populations, B/FTC/TAF was statistically noninferior to the comparator (Study 1489: ABC/DTG/ 3TC; Study 1490: DTG + FTC/TAF). In both studies, the lower bound of the CI did not exceed the a priori noninferiority margin of –12%. In Study 1489, the difference in the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 was –0.6% (95% CI, –4.8% to 3.6%). Noninferiority was confirmed in the PP analysis. In Study 1490, the difference in the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 was –3.5% (95% CI, –7.9% to 1.0%). Noninferiority was confirmed in the PP analysis. While B/FTC/TAF was statistically noninferior to the comparator regimens in both trials, the percentage of B/FTC/TAF patients achieving virologic success in Study 1490 (89.4%) was lower than expected, based on the assumptions for the sample size calculation, and the clinical expert consulted for this review also considered this lower than expected. No specific characteristics of the patient population in Study 1490 were thought to explain the lower success rate. In addition, the proportion of patients categorized as having HIV-1 RNA ≥ 50 copies/mL at week 48 was higher in the B/FTC/TAF group (4.4%) versus DTG + FTC/TAF (1.2%) in Study 1490. However, it was noted that in Study 1489 the data for virologic failure favoured B/FTC/TAF.

Quality of life, as measured by the SF-36, was reported for Study 1489 but was an exploratory outcome only. The change in the two subscores of the SF-36, PCS and MCS, were not significantly different between the B/FTC/TAF group and the ABC/DTG/3TC group.

In Study 1489, mean adherence was [redacted] and [redacted] in the B/FTC/TAF group and in the ABC/DTG/3TC group, respectively. However, the proportion of patients with 95% or higher adherence was numerically higher in the B/FTC/TAF group ([redacted]) compared with the ABC/DTG/3TC group ([redacted]). In Study 1490, mean adherence was [redacted] and [redacted] in the B/FTC/TAF group and in the DTG + FTC/TAF group, respectively. The proportion of patients with 95% or higher adherence was [redacted] in the B/FTC/TAF group and the [redacted] in the DTG + FTC/TAF group. STRs may be expected to improve adherence compared with multi-tablet regimens; however, this was not demonstrated in Study 1490. The use of a double dummy increased the number of tablets that were taken by participants, which may have limited the ability to identify adherence benefits of a daily STR in Study 1490, regardless of the fact that adherence was measured only in the active treatments.

Treatment-Experienced/Switch

In the treatment-experienced/switch populations, B/FTC/TAF was noninferior to the comparators in each study. In all three studies, the upper bound of the CI did not exceed the a priori noninferiority margin of 4%. The difference in the proportion of patients with HIV-1 RNA ≥ 50 copies/mL at week 48 was 0.7% in Study 1844 (95% CI, –1.0% to 2.8%); 0.0% in Study 1878 (95% CI, –2.5% to 2.5%) and 0.0% in Study 1961 (95% CI –2.9% to 2.9%). Noninferiority was confirmed in the PP analysis of all studies.

HRQoL, as measured by the SF-36, was reported for Study 1844. The two subscores of the SF-36, PCS and MCS, did not change appreciably from baseline, which was not unexpected, given that patients were receiving ART at baseline; change from baseline was not significantly different between the B/FTC/TAF group and the ABC/DTG/3TC group.

In Study 1844, mean adherence was [redacted] and [redacted] in the B/FTC/TAF and ABC/DTG/3TC groups, respectively. The proportion of patients reporting 95% or higher adherence was [redacted] in the B/FTC/TAF group and [redacted] in the ABC/DTG/3TC group. In Study 1878, adherence was reported only for the B/FTC/TAF group. Mean adherence in the B/FTC/TAF group was [redacted] and [redacted] reported 95% or higher adherence. In Study 1961, mean adherence was [redacted] and [redacted] in the B/FTC/TAF and SBR (E/C/FTC/TAF or E/C/FTC/TD or ATV + RTV + FTC/TDF) groups, respectively. The proportion of patients reporting 95% or higher adherence was [redacted] (B/FTC/TAF) and [redacted] (SBR: E/C/FTC/TAF or E/C/FTC/TDF or ATV + RTV + FTC/TDF). Adherence was numerically higher in the treatment-experienced/switch studies compared with the treatment-naive studies. This is expected, as patients enrolled in the treatment-experienced/switch studies had to be virologically suppressed on the current ARV regimen, indicating that they had a high degree of adherence and tolerability at study entry.

Harms

In the treatment-naive population, the majority of the study population experienced at least one AE (82.5% to 89.8%). AEs were balanced across treatment groups. The most frequent AEs (> 10% of patients) were diarrhea, headache, and nausea. There was one death (Study 1490, DTG + FTC/TAF group). A small proportion of patients withdrew from the study due to AEs (Study 1489: none in the B/FTC/TAF group versus four [1.3%] in the ABC/DTG/3TC group; Study 1490: five (1.6%) in the B/FTC/TAF group, versus one (0.3%) in the DTG + FTC/TAF group. No patients developed treatment-emergent drug resistance. With respect to renal-related harms, in both studies, serum creatinine increased slightly from baseline to week 48. However, week 48 serum creatinine was still within normal range. In both studies, eGFR decreased from baseline to week 48, slightly more so in the comparator arms containing DTG. The clinical expert indicated that this is a known side effect of DTG. However, it should be noted that both trials excluded patients with moderate renal impairment. With respect to bone-related harms, neither study revealed any clinically meaningful change in BMD at the hip or spine.

In the treatment-experienced/switch population, the majority of the study population experienced at least one AE (67.4% to 80.3%). AEs were balanced across treatment groups. The most frequent AEs (> 10% of patients) were upper respiratory tract infection and nasopharyngitis. There were five deaths (two in Study 1844; two in Study 1878; and one in Study 1961). A small proportion of patients withdrew from the study due to AEs (eight [1.4%] in Study 1844; four [0.7%] in Study 1878; and none in Study 1961). No patients in Study 1844 developed treatment-emergent drug resistance. In Study 1878, one patient in the SBR group (on a regimen of RTV-boosted DRV + ABC/3TC) developed L74V in reverse transcriptase. In Study 1961, one patient in the SBR group (E/C/FTC/TAF) developed M184M/I/V. With respect to renal-related harms, in the three studies, the effect of B/FTC/TAF relative to comparators was inconsistent; however, at week 48, renal function continued to be within normal range for all studies across all treatment groups. With respect to bone-related harms, the three studies did not reveal any clinically meaningful change in BMD at the hip or spine.

A numerically larger proportion of patients in the treatment-naive trials experienced an AE (82% to 90%) compared with the treatment-experienced/switch patients (65% to 80%). Similarly, a numerically larger proportion of patients in the treatment-naive trials experienced an SAE (6.1% to 12.2%) compared with the treatment-experienced /switch patients (3% to 7.8%). The notable harms identified in the systematic review protocol were,

overall, experienced by a similar proportion of patients in the B/FTC/TAF group and the comparator group within each trial. However, there are two exceptions. In Study 1489, 10.2% and 22.9% experienced nausea in the B/FTC/TAF group and the ABC/DTG/3TC groups, respectively. In Study 1878, 12.1% and 4.2% of patients experienced headache in the B/FTC/TAF group and the RTV- or COBI-boosted ATV or DRV + FTC/TDF or ABC/3TC groups, respectively. Differences in the latter trial (Study 1878) would be expected, given that patients in the comparator arm had been stabilized on their prior treatment for at least six months and were presumably tolerating treatment. Patients (Appendix 1: Patient Input Summary) and the clinical expert consulted for this review did not identify any specific harms to be addressed in this review.

Based on Studies 1489 and 1490, the DHHS recently issued a statement regarding B, recommending B/FTC/TAF 50 mg/25 mg/200 mg once daily as one of the initial regimens for most people with HIV.[5]

Indirect Treatment Comparisons

The direct evidence of the comparative efficacy and safety of B/FTC/TAF in treatment-naive patients is limited to comparisons with DTG/ABC/3TC and DTG + FTC/TAF, both of which are recommended by the DHHS as initial regimens for most people with HIV. However, direct comparisons between B/FTC/TAF and other recommended initial treatments (e.g., E/C/FTC/TAF, E/C/FTC/TDF, or raltegravir + FTC/TDF or FTC/TAF) are also of interest. Further, direct comparative evidence of the efficacy and safety of switching to B/FTC/TAF from other regimens in virologically suppressed patients is limited, given that neither Study 1878 or Study 1961 provided virologic outcomes based on the specific baseline regimen, and the most commonly used agents in Study 1878 are no longer commonly used regimens, according to the clinical expert. Thus, the manufacturer assessed the feasibility of conducting a network meta-analysis to provide indirect evidence that could address the above evidence gaps.

[redacted]However, given a number of limitations, the network meta-analysis does not provide compelling evidence that the safety and efficacy of B/FTC/TAF [redacted]

Potential Place in Therapy[2]

The triple co-formulation B/FTC/TAF is the eighth STR to become available on the Canadian market (preceded by Atripla, Complera, Odefsey, Stribild, Genvoya, Triumeq, and Juluca).

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

Although treatment alternatives are welcome, there are no significant unmet needs for patients with a nonresistant virus in this era of HIV ART. The available antivirals offer STR options for the majority of HIV-infected persons with nonresistant virus. They are convenient and increasingly free of immediate and long-term toxicity. Drug interactions can occur but are manageable in most cases.

When patients adhere to therapy and take it as recommended (for instance, with food or without antacids), most of the available STRs suppress HIV replication in the vast majority of treated patients. The strength of B/FTC/TAF is its simplicity of use. There are very few expected side effects (unlike Atripla), little renal or bone toxicity (unlike Atripla, Complera, and Stribild), no significant drug–drug interactions (unlike Genvoya or Stribild), no dietary restrictions (unlike Atripla, Complera, Odefsey, and Juluca), and no need for pre-testing for HLA B5701 (unlike Triumeq).

Because it avoids the concerns of other regimens, B/FTC/TAF may be prescribed immediately upon diagnosis with little concern for intolerance, inconvenience, or toxicity. It may be used as a substitute for any of the above options in cases of toxicity or inconvenience.

B/FTC/TAF would be a reasonable treatment option for almost any patient with a nonresistant virus. It can be taken at any time of day, with or without food, by patients with other comorbidities and on other medications. It may be very commonly prescribed as first-line therapy or as a switch medication (except in the case of virologic treatment failure) and may become the preferred therapy for most patients with nonresistant virus because of its ease of use.

Conclusions

In two randomized controlled trials conducted in treatment-naive patients with HIV-1, B/FTC/TAF was demonstrated to be noninferior to ABC/DTG/3TC and to DTG + FTC/TAF in achieving virologic suppression (HIV-1 RNA < 50 copies/mL) at week 48. In three randomized controlled trials conducted in treatment-experienced patients with virologically suppressed HIV-1, B/FTC/TAF was demonstrated to be noninferior to continuing treatment with (1) ABC/DTG/3TC, (2) RTV- or COBI-boosted ATV or DRV + either FTC/TDF or ABC/3TC, (3) E/C/FTC/TAF, (4) E/C/FTC/TDF, or (5) ATV + RTV + FTC/TDF, in terms of the proportion of patients experiencing virologic failure (HIV-1 RNA ≥ 50 copies/mL) at week 48. Harms were similar between treatment groups, and surrogates for renal and bone safety were unremarkable at week 48. Longer-term data are needed to the support the comparative efficacy and safety of B/FTC/TAF.

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 non-governmental organization that focuses on access to treatment as well as care and support for patients living with HIV and hepatitis C (HCV) in Canada. Its goals are to maintain a dialogue with community members, service providers, policy-makers, and other relevant stakeholders to identify, develop, and implement policy and program solutions. Full CTAC membership is reserved for (a) individual people living with HIV (including HCV coinfection), and (b) organizations, groups, or projects with a substantial HIV mandate (including HCV coinfection). Associate CTAC membership is open to any individual, organization, group, or project that supports CTAC's mandate and objectives.

Upon disclosure, the CTAC claimed to have received funding from ViiV Healthcare in excess of $50,000 within the past two years. They acknowledge that they have not received any help from outside their patient group to collect or analyze data or for the completion of this submission.

2. Condition-Related Information

The information for this submission is a summary of a patient input consultation workshop in Toronto, Canada (attended by six people living with HIV), and survey data collected for the patient submission on dolutegravir and a dolutegravir and rilpivirine combination. Patients who attended the consultation workshop ranged in age from their 40s to 60s and had been receiving HIV treatment between 18 and approximately 34 years.

Patients with HIV generally manage their condition as a chronic illness; however, they are more susceptible to inflammation and noninfectious comorbidities, including bone fractures and renal failure, at earlier ages. There are many negative mental health outcomes that have been associated with those living with HIV, whether as a side effect from treatment, or from facing stigma, discrimination, and related stress. Stigma is one of the more prominent issues dealt with, as explained by one respondent: "My quality of life has improved, but there's still stigma, especially from family members. I learned to hide my HIV medications." This is further highlighted by another respondent's explanation of how they deal with the care they receive from the medical community: "Local doctors feel ill-equipped to treat HIV due to inexperience because of low patient caseloads with the condition. Stigma also plays into it I think. Unless they're familiar, doctors still see HIV as something more difficult to live with than it actually is." Another respondent (from the dolutegravir and rilpivirine survey) discussed the challenge of managing HIV while residing in a rural area: "I live in a rural area and have to travel about 100 km each way for my doctor's appointments. I only see my doctor about every six months. Obviously, if I had to travel that far more often, it would be a challenge. For those who don't have the support of family, this could definitely be an obstacle."

Many of those living with HIV experience intersecting vulnerabilities conditioned by the social determinants of health — the social and structural conditions in which people live, work, and are shaped by the distribution of money, power, and resources. The following quotations highlight these vulnerabilities:

"My challenges are not treatment-related but more about how I am treated, because I work periodically and I access Trillium. The Trillium plan is a barrier for people who work part-time or periodically. AIDS organizations and the government itself often assume that people will go onto ODSP or have private drug plans." (Respondent from dolutegravir and rilpivirine survey)

"I had an excellent job, which came with an excellent health plan where the best HIV medications available were covered. I was so, so thankful for that. I think it made all the difference when I was diagnosed and first started treatment. I know that there are many who aren't so lucky."

Respondents all noted substantial impact on caregivers looking after patients living with HIV. One respondent highlighted the challenges his/her spouse faces in providing support while dealing with disclosure. According to the respondent, "hiding from friends and some of our family members that I am HIV positive" has been extremely difficult and has hindered the respondent's ability to acquire a social safety net.

3. Current Therapy-Related Information

Findings from the survey indicate that from the six respondents who identified as living with HIV are all currently, or have previously been, on treatment for HIV. Their length of time on current therapy ranged from four months to eight years. Considering that the survey population was made up primarily of long-term survivors (ranging between 18 to 34 years), this result demonstrates that treatment regimens change somewhat often for people living with HIV. This emphasizes the significant need for the availability of several HIV treatments.

All survey respondents indicated current or past use of regimens containing darunavir, dolutegravir, emtricitabine, and/or tenofovir. Reported treatment regimens included Prezista (darunavir), Intelence (etravirine), Isentress (raltegravir), Norvir (ritonavir), and/or Atripla (efavirenz/emtricitabine/tenofovir), with different combinations of these being used. Of all the treatments patients reported taking, all noted that their treatment (both old and new) was effective at suppressing their viral load; however, one respondent stated that they experienced significant effects from the older treatments when they first began their regimens, "When I was first diagnosed, my doctor forced me onto AZT. AZT made me extremely sick. I became anemic and had extremely low energy. The side effects were so bad that I wanted to discontinue treatment."

In the survey, respondents noted staff time, funding, transportation, and other associated costs posed barriers to receiving support. These factors also have an impact on treatment adherence, mental health, and other determinants of health. One respondent noted the challenges associated with lack of funding for direct support: "We have to decrease our direct support services, and in PEI there are very little services for PHAs in many areas, including addictions, mental health, housing, and food securing, which put treatment lower on the priority list." In addition, one respondent noted that difficulties understanding stigma and its impact, and navigating HIV-specific social services and institutional systems, including disability, insurance, and mortgage, have presented specific challenges.

4. Expectations About the Drug Being Reviewed

No survey respondents had experience with the single-dose, combination drug bictegravir/emtricitabine/tenofovir alafenamide. However, many respondents expressed interest in this combination because of its benefits, including smaller pill size and the ability to take the medication with or without food. One respondent viewed the potential benefits as less persuasive, saying, “I don’t see replacing the “devil” I know with the “devil” I don’t know, at least on a personal basis, if I had to make changes. And that time could come, since I’ve been on the present regimen for quite some time.”

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 30, 2018
Alerts:	Weekly search updates until Sept 19, 2018.
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#	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	Publication type
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; MEDLINE ALL
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

#	Searches
1	(biktarvy* or bftaf).ti,ab,kf,ot,hw,rn,nm.
2	(Bictegravir* or GS-9883 or GS9883 or GS988301 or 8GB79LOJ07).ti,ab,kf,ot,hw,rn,nm.
3	Emtricitabine/
4	(emtricitabin* or emtriva* or coviracil* or racivir* or 524W91 or "BW 1592" or BW1592 or "BW 524w91" or "BW 524 w 91" or BW524W91 or "BW 524W" or BW524W or "DRG 0208" or DRG0208 or "psi 5004" or psi5004 or "HSDB 7337" or HSDB7337 or G70B4ETF4S or FTC).ti,ab,kf,ot,kw,hw,rn,nm.

MULTI-DATABASE STRATEGY	
#	**Searches**
5	3 or 4
6	tenofovir/
7	(tenofovir* or vemlidy* or GS 7340 or GS7340 or EL9943AG5J or TAF or PMPA).ti,ab,kf,ot,kw,hw,rn,nm.
8	6 or 7
9	2 and 5 and 8
10	1 or 9
11	10 use
12	bictegravir plus emtricitabine plus tenofovir alafenamide/
13	(biktarvy* or bftaf).ti,ab,kw,dq.
14	12 or 13
15	*Bictegravir/
16	(Bictegravir or GS-9883 or GS9883 or GS988301).ti,ab,kw,dq.
17	15 or 16
18	*emtricitabine/
19	(emtricitabin* or emtriva* or coviracil* or racivir* or 524W91 or "BW 1592" or BW1592 or "BW 524w91" or "BW 524 w 91" or BW524W91 or "BW 524W" or BW524W or "DRG 0208" or DRG0208 or "psi 5004" or psi5004 or "HSDB 7337" or HSDB7337 or FTC).ti,ab,kw,dq.
20	18 or 19
21	*tenofovir alafenamide/
22	*tenofovir/
23	(tenofovir* or vemlidy* or GS 7340 or GS7340 or TAF or PMPA).ti,ab,kw,dq.
24	or/21-23
25	17 and 20 and 24
26	14 or 25
27	26 use oemezd
28	27 not conference abstract.pt.
29	11 or 28
30	remove duplicates from 29

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:	May 2018
Keywords:	Biktarvy, BFTAF, bictegravir/emtricitabine/tenofovir alafenamide, HIV-1
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

No studies identified for full-text review were excluded from the review.

Appendix 4: Detailed Outcome Data

Table 23: Other Efficacy Outcomes: Treatment-Experienced/Switch

Other Efficacy Outcomes, N (%)	Study 1844		Study 1878		Study 1961[b]	
	B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (N = 287)	B/FTC/TAF (N = 234)	SBR (N = 236)
Development of Drug Resistance						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with Integrase data at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary INSTI-R[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average number of primary INSTI-R mutations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary INSTI-R[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average number of secondary INSTI-R mutations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with PR/RT data at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary NRTI-R[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average number of primary NRTI-R mutations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary NNRTI-R[g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average number of NNRTI-R mutations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary PI-R[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Other Efficacy Outcomes, N (%)	Study 1844		Study 1878		Study 1961[b]	
	B/FTC/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/FTC/TAF (N = 290)	SBR (N = 287)	B/FTC/TAF (N = 234)	SBR (N = 236)
Average number of PI-R mutations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resistance Category						
RAP (% of FAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with data (any gene)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who resuppressed HIV-1 RNA < 50 copies/mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final RAP[i] (% of FAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with data (any gene)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Developed resistance mutations to study drugs (% of FAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Developed resistance mutations to study drugs (% of final RAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Developed any INSTI-R[j]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Developed primary NRTI-R[k]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Developed primary NNRTI-R[l]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Developed primary PI-R[m]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; FAS = full analysis set; INSTI = integrase strand transfer inhibitor; NA = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; R = resistance; RAP = resistance analysis population; RNA = ribonucleic acid; RT = reverse transcriptase; SBR = stay on baseline regimen; TAM = thymidine analogue mutation.

[redacted]

Source: Clinical Study Reports Study 1844, Study 1878, Study 1961.

Appendix 5: Validity of Outcomes

Aim

To summarize the validity of the following outcome measures:

- Short Form (36) Health Survey (SF-36) version 2 (v2).

Findings

Table 24: Validity and Minimal Clinically Important Difference of Outcome Measure

Instrument	Type	Evidence of Validity	MCID	References
SF-36	General health status instrument that contains a PCS and MCS	Yes	2 points in SF-36 PCS 3 points in SF-36 MCS	Maruish, 2011[36]

MCID = minimal clinically important difference; MCS = physical component summary; PCS = physical component summary; SF-36 = Short Form (36) Health Questionnaire.

Short Form (36) Health Survey Version 2

The SF-36 (with v2 being the most up-to-date version) is a 36-item general health status instrument that has been used extensively in clinical trials in many disease areas.[37] The SF-36 consists of eight health domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH).[37-39] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status.[37,38] The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation (SD) of 10 in the general US population. Therefore, all scores above/below 50 are considered above/below average for the general US population.

The SF-36 was observed to be both valid and reliable in patients with HIV.[40] In a multi-centre AIDS Cohort Study of 2,295 homosexual and bisexual men who were HIV-positive, the internal consistency reliability was good (ranging between 0.85 to 0.86).[40] The exploratory factor analysis for the SF-36 provided evidence of a separate physical and mental health factor, similar to that observed in both the general population and for other disease states.[40]

In terms of determining whether serostatus had any relationship with health-related quality of life (HRQoL), Bing et al. observed that the SF-36 MH domain was not affected by serostatus, whereas the GH perception scale and PCS score were worse in seropositive participants who were asymptomatic or who had CD4+ lymphocytes greater than or equal to 500/mm^3 compared with seronegative participants.[40] In addition, it was observed that significant decreases in HRQoL scores were observed in patients with only one HIV-related symptom; however, this same decrease in HRQoL was not observed in patients with more than one HIV-related symptom or AIDS.[40] While this study included a large sample, the results may not be generalizable to women, ethnic minorities, injection drug users, youth, or other homosexual or bisexual men who are less motivated to participate in a study.[40] Call et al.[41] also observed an association between increased CD4+ cell counts and better PCS

scores of the SF-36, particularly in the PF, GH, RP, and VT subscales. However, this study included a small sample that precluded any further stratified or adjusted analyses.[41]

In terms of the association between viral load and HRQoL, Call et al.[41] observed a consistent association between worse scores on the PCS of the SF-36 and increased viral load, particularly in the PF, RP, BP, GH, RE, and VT subscores.

In a literature review, Clayson et al.[42] set out to examine HRQoL measures used in HIV/AIDS clinical trials. The SF-36 was determined to be worth considering for use alongside disease-specific measures, as it has the most evidence associated with its use when compared with other generic measures (including the EuroQol 5-Dimensions [EQ-5D] questionnaire and the Health Utilities Index).[42] However, its length was determined to be problematic.[42]

On any of the scales, an increase in score indicates improvement in health status. In general use, a change of two points in the SF-36 PCS and three points in the SF-36 MCS indicates a clinically meaningful improvement, as determined by the patient.[36] Based on anchor data, the SF-36 User's Manual also proposed the following minimal mean group differences, in terms of t score points, for SF-36 v2 individual dimension scores: PF, 3; RP, 3; BP, 3; GH, 2; VT, 2; SF, 3; RE, 4; and MH, 3. It should be noted that these minimally important difference (MID) values were determined as appropriate for groups with mean t score ranges of 30 to 40. For higher t score ranges, MID values may be higher.[36] The minimal clinically important difference (MCID) for either the PCS or MCS of the SF-36 has been determined to be typically between 2.5/3 and 5 points.[38,43,44] No specific MCID or MCID range has been specifically determined for patients with HIV.

Appendix 6: Summary of Network Meta-Analysis

Introduction

The following is a summary and critical appraisal of the methods and main findings of the manufacturer-provided network meta-analysis (NMA), which evaluated the comparative efficacy of a fixed-dose combination of bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (B/FTC/TAF) versus various comparators (standard of care, including numerous anti-HIV regimens in co-formulation or co-administered individually at the recommended doses) in the treatment of patients with HIV infection.[45]

Methods

Systematic Review

[redacted]

Table 25: [redacted]

[redacted]

Source: B/FTC/TAF NMA report.[45]

Network Meta-analysis

[redacted]

[redacted]

Table 26: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]
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[redacted]		[redacted]	[redacted]

[redacted]

Source: B/FTC/TAF NMA report.[45]

Table 27: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: B/FTC/TAF NMA report.[45]

Efficacy Outcomes

[redacted]

[redacted]

Figure 3:

Source: B/FTC/TAF NMA report.[45]

Table 28:

Source: B/FTC/TAF NMA report.[45]

Safety Outcomes

Figure 4:

Source: B/FTC/TAF NMA report.[45]

[redacted]

Table 29: [redacted]

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[redacted]

Source: B/FTC/TAF NMA report.[45]

[redacted]

[redacted]

Figure 5: [redacted]

[redacted]

Source: B/FTC/TAF NMA report.[45]

Table 30: [redacted]

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[redacted]

Source: B/FTC/TAF NMA report.[45]

[redacted]

Critical Appraisal of Network Meta-Analysis

The quality of the manufacturer-submitted NMA was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons,[46] and commentary for each of the relevant items identified by ISPOR is provided in Table 31.

Strengths

[redacted]

Limitations

[redacted]

[redacted]

[redacted]

Conclusion

[redacted] However, given a number of limitations, the NMA does not provide compelling evidence that the safety and efficacy of B/FTC/TAF [redacted]

Table 31: Appraisal of Network Meta-Analysis Using ISPOR Criteria

ISPOR Checklist Item[46]		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	[redacted]
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	[redacted]
3.	Are the outcome measures described?	[redacted]
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	[redacted]
5.	Are sensitivity analyses presented?	[redacted]
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	[redacted]
7.	Does the study describe an assessment of model fit?	[redacted]
8.	Are the results of the evidence synthesis presented clearly?	[redacted]
9.	Sensitivity/scenario analyses	[redacted]

References

1. AIDS Info: Understanding HIV / AIDS. Rockville (MD): AIDSinfo; 2018 Jul 30: https://aidsinfo.nih.gov/understanding-hiv-aids. Accessed 2018 Jul 30.
2. Health Canada, Public Health Agency of Canada. HIV/AIDS. Ottawa: Government of Canada; 2018 Jul 28: https://www.canada.ca/en/public-health/services/diseases/hiv-aids.html. Accessed 2018 Jul 30.
3. HIV and AIDS in Canada: Surveillance Report to December 31, 2014. Ottawa: Public Health Agency of Canada; 2015 Nov 27: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/hiv-aids-canada-surveillance-report-december-31-2014.html. Accessed 2018 Jul 30.
4. Guidelines for the use of antiretroviral agens in adults and adolescents living with HIV. Rockville (MD): AIDSinfo; 2018 May 30: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0. Accessed 2018 Jul 30.
5. Department of Health and Human Services Adults and Adolescents Antiretroviral Guidelines Panel* Classifies a Fixed-Dose Combination Product of Bictegravir/Tenofovir Alafenamide/Emtricitabine as One of the Recommended Initial Regimens for Most People with HIV. Rockville (MD): AIDSinfo; 2018 Mar 27: https://aidsinfo.nih.gov/news/2044/adult-arv-panel-classifies-bic-taf-ftc-as-recommended-initial-regimen-for-hiv. Accessed 2018 Jul 31.
6. Clinical Study Report: 1489. A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naive Adults [**CONFIDENTIAL** internal manufacturer's report]. Foster City, CA: Gilead Sciences, Inc.; 2017 May 24.
7. Clinical Study Report: 1490. A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults [**CONFIDENTIAL** internal manufacturer's report]. Foster City (CA): Gilead Sciences, Inc.; 2017 May 24.
8. Clinical Study Report: 1844. A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed [**CONFIDENTIAL** internal manufacturer's report]. Foster City (CA): Gilead Sciences, Inc.; 2017 May 23. Accessed 2017 May 23.
9. Clinical Study Report: 1878. A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults [**CONFIDENTIAL** internal manufacturer's report]. Foster City (CA): Gilead Sciences, Inc.; 2017 May 26. Accessed 2017 May 26.
10. Clinical Study Report: 1961. A Phase 3, Randomized, Open Label Study to Evaluate the Safety and Efficacy of Switching to a Fixed Dose Combination (FDC) of GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) from Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF), Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (E/C/F/TDF) or Atazanavir + Ritonavir + Emtricitabine/Tenofovir Disoproxil Fumarate (ATV+RTV+FTC/TDF) in Virologically Suppressed HIV-1 Infected Women [**CONFIDENTIAL** internal manufacturer's report]. Foster City (CA): Gilead Sciences, Inc.; 2018 Feb 7. Accessed 2018 Feb 07.
11. HIV/AIDS. Atlanta (GA): US Centre for Disease Control; 2018 Jul 24: https://www.cdc.gov/hiv/. Accessed 2018 Jul 30.
12. <Biktarvy> (bictegravir/emtricitabine/tenofovir alafenamide) tablets [product monograph]. Mississauga (ON): Gilead Sciences Canada; 2018.
13. Triumeq (dolutegravir sodium—abacavir sulfate—lamivudine) [product monograph]. Laval (QC): ViiV Healthcare ULC; 2018 Apr 10: www.e-therapeutics.ca.
14. e-CPS. Ottawa: Canadian Pharmacists Association; 2018: https://www.e-therapeutics.ca.
15. RxFiles drug comparison charts: HIV: human immunodeficiency virus. Vol 2018. 11th ed. Saskatoon: RxFiles; March 2017: http://www.rxfiles.ca/rxfiles/uploads/documents/ChartsTitlePage-11th-edition-2017-book-references.pdf. Accessed 2018 Jul 30.
16. Pr Genvoya® (elvitegravir—cobicistat—emtricitabine—tenofovir alafenamide hemifumarate) [product monograph]. Foster City (CA): Gilead Sciences; 2018 Apr 12: www.e-therapeutics.ca.
17. Pharmacist's Letter. Tenofovir: Alafenamide vs Disoproxil Fumarate. Stockton (CA): Therapeutic Research Center; 2016.
18. Odefsey (emtricitabine—rilpivirine HCl—tenofovir alafenamide hemifumarate) [product monograph]. Foster City (CA): Gilead Sciences; 2018 Jan 15: www.e-therapeutics.ca.
19. Juluca® (dolutegravir sodium—rilpivirine HCl) [product monograph]. Laval (QC): ViiV Healthcare ULC; 2018 May 17: https://pdf.hres.ca/dpd_pm/00045436.PDF.
20. Symtuza (darunavir ethanolate—cobicistat—emtricitabine—tenofovir alafenamide hemifumarate) [product monograph]. Beerse (BE): Janssen; 2018 Mar 7: www.e-therapeutics.ca.
21. Stribild (elvitegravir—cobicistat—emtricitabine—tenofovir disoproxil fumarate) [product monograph]. Foster City (CA): Gilead Sciences; 2018 Apr 12: www.e-therapeutics.ca.
22. Complera® (emtricitabine—rilpivirine HCl—tenofovir disoproxil fumarate) [product monograph). Foster City (CA): Gilead Sciences; 2017 Jun 7: www.e-therapeutics.ca.
23. Atripla® efavirenz—emtricitabine—tenofovir disoproxil fumarate [product monograph]. Foster City (CA): Gilead Sciences; 2018 Mar 20: www.e-therapeutics.ca.

24. Prezcobix® (darunavir ethanolate—cobicistat). Beerse (BE): Janssen; 2018 May 23: www.e-therapeutics.ca.
25. Descovy® (emtricitabine—tenofovir alafenamide hemifumarate) [product monograph]. Foster City (CA): Gilead Sciences; 2018 Feb 13: www.e-therapeutics.ca.
26. Tivicay (dolutegravir sodium) [product monograph]. Laval (QC): ViiV Healthcare ULC; 2018 May 18: www.e-therapeutics.ca.
27. Prezista (darunavir ethanolate) [product monograph]. Beerse (BE): Janssen; 2017 Oct 20: www.e-therapeutics.ca.
28. Norvir® (ritonavir) [product monograph]. North Chicago (IL): AbbVie; 2017 Nov 27: www.e-therapeutics.ca.
29. Truvada (emtricitabine—tenofovir disoproxil fumarate) [product monograph]. Foster City (CA): Gilead Sciences; 2017 May 30: www.e-therapeutics.ca.
30. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet.* 2017;390(10107):2063-2072.
31. Wohl D, Clarke A, Maggiolo F, et al. Patient-Reported Symptoms Over 48 Weeks Among Participants in Randomized, Double-Blind, Phase III Non-inferiority Trials of Adults with HIV on Co-formulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide versus Co-formulated Abacavir, Dolutegravir, and Lamivudine. *Patient.* 2018 Jun 29. https://www.ncbi.nlm.nih.gov/pubmed/29956087 [Epub ahead of print].
32. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet.* 2017;390(10107):2073-2082.
33. Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV.* 2018.
34. Daar ES, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV.* 2018;5(7):e347-e356.
35. Gilead Sciences response to July 11, 2018 CDR request for additional information regarding the BFTAF CDR review [CONFIDENTIAL additional manufacturer's information]. Mississauga (ON): Gilead Sciences Canada; 2018 Jul 13.
36. Maruish ME. User's manual for the SF-36v2 health survey. 3rd ed. ed. Lincoln (RI): Quality Metric Inc; 2011.
37. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical care.* 1992;30(6):473-483.
38. Arends M, Hollak CE, Biegstraaten M. Quality of life in patients with Fabry disease: a systematic review of the literature. *Orphanet journal of rare diseases.* 2015;10:77.
39. Mease PJ, Menter MA. Quality-of-life issues in psoriasis and psoriatic arthritis: outcome measures and therapies from a dermatological perspective. *Journal of the American Academy of Dermatology.* 2006;54(4):685-704.
40. Bing EG, Hays RD, Jacobson LP, et al. Health-related quality of life among people with HIV disease: results from the Multicenter AIDS Cohort Study. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2000;9(1):55-63.
41. Call SA, Klapow JC, Stewart KE, et al. Health-related quality of life and virologic outcomes in an HIV clinic. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2000;9(9):977-985.
42. Clayson DJ, Wild DJ, Quarterman P, Duprat-Lomon I, Kubin M, Coons SJ. A comparative review of health-related quality-of-life measures for use in HIV/AIDS clinical trials. *Pharmacoeconomics.* 2006;24(8):751-765.
43. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *PharmacoEconomics.* 1999;15(2):141-155.
44. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Annals of medicine.* 2001;33(5):350-357.
45. Systematic Literature Review and Network Meta-Analysis of Clinical Studies for B/F/TAF and Comparators for the Treatment of HIV Infection [CONFIDENTIAL internal manufacturer's report]. Cambridge (GB): Costello Medical; 2018 Jan.
46. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health.* 2011 Jun;14(4):417-428.