CADTH

CADTH COMMON DRUG REVIEW

Common Drug Review New Combination Product Submission

Darunavir/Cobicistat/Emtricitabine/Tenofovir alafenamide (Symtuza)

(Janssen Canada Inc.)

Indication: A complete regimen for the treatment of HIV type 1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with no known mutations associated with resistance to the individual components of Symtuza.

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CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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Abbreviations

AE	adverse event
ART	antiretroviral therapy
AUC	area under the plasma concentration-time curve
AUC_{24h}	area under the plasma concentration-time curve over the 24-hour dosage interval
AUC_{tau}	area under the plasma concentration-time curve over the dosage interval
BMD	bone mineral density
bPI	boosted protease inhibitor
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
C_{max}	maximum observed concentration
COBI or C	cobicistat
DRV or D	darunavir
E	elvitegravir
FAS	full analysis set
FDC	fixed-dose combination
FTC or F	emtricitabine
HIV-1	HIV type 1
ITT	intention-to-treat
LPV	lopinavir
MH	Mantel–Haenszel
MTR	multiple-tablet regimen
NDS	new drug submission
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
PK	pharmacokinetic
PP	per-protocol
RBP	retinol-binding protein
RCT	randomized controlled trial
RNA	ribonucleic acid
rtv	ritonavir
SAE	serious adverse event
SD	standard deviation
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
T_{max}	time since study drug administration until the maximum observed analyte concentration

Drug	darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza)
Indication	Indicated for a complete regimen for the treatment of HIV type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with no known mutations associated with resistance to the individual components of Symtuza
Listing Request	As per indication
Manufacturer	Janssen Canada Inc.

Executive Summary

This report contains references provided by the manufacturer as well as by CADTH. Square brackets have been placed around CADTH's references for the purpose of distinguishing the sources of these references.

Introduction

HIV is a chronic condition that can be managed through treatment with antiretroviral therapy (ART). The current goals of treatment are to suppress viral replication to prevent disease progression, HIV-related morbidity, and mortality; to restore or preserve immunologic function; and to prevent onward transmission of the virus. Early ART regimens were associated with high pill burdens and/or complex administration protocols. In addition, aging of the population of patients with HIV means increased pill burden for the treatment of comorbid conditions that become more common with age. Since ART is not curative and must be taken indefinitely to maintain virologic suppression, adherence to ART is important. High pill burdens and complex administration regimens have been linked to lower adherence. Therefore, any strategies that simplify administration and/or minimize pill burden, such as single-tablet regimens (STRs) containing fixed-dose combinations (FDCs), may lead to better adherence to ART in people living with HIV infection.

Symtuza is a four-drug STR product consisting of the following:

- 800 mg duranavir (DRV or D), a protease inhibitor (PI)
- 150 mg cobicistat (COBI or C), a pharmaco-enhancing drug
- 200 mg emtricitabine (FTC or F), a nucleoside reverse transcriptase inhibitor
- 10 mg tenofovir alafenamide (TAF), a nucleotide reverse transcriptase inhibitor.

A Notice of Compliance for darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF), as a complete regimen for the treatment of HIV type 1 (HIV-1) infection in adults and adolescents with no known mutations associated with resistance to the individual components of D/C/F/TAF, was granted by Health Canada on March 8, 2018.[1] The recommended dosage of D/C/F/TAF FDC is one tablet taken orally once daily with food.

This submission for D/C/F/TAF FDC was filed as a new FDC product, based on the fact that DRV/COBI (Prezcobix) and FTC/TAF (Descovy) received CADTH Canadian Drug Expert Committee (CDEC) recommendations to reimburse with conditions in 2015 and 2016, respectively. DRV/COBI is currently funded by a majority of the CADTH Common Drug Review (CDR)-participating drug plans, while FTC/TAF is reimbursed only in British Columbia and by Veterans Affairs Canada.

The objective of this review is to conduct an appraisal of the clinical evidence and pharmacoeconomic evaluation submitted by the manufacturer.

Included Studies

Evidence of the efficacy and safety of D/C/F/TAF FDC in the target population was identified in three randomized controlled trials (RCTs) provided in the manufacturer's submission: one phase II study (GS-US-299-0102) and two phase III studies (AMBER and EMERALD). In GS-US-299-0102 (N = 153) and AMBER (N = 725), the efficacy and safety of D/C/F/TAF (800 mg/150 mg/200 mg/10 mg) FDC once daily were compared with co-administration of DRV 800 mg + COBI 150 mg + F/TDF (200 mg/300 mg) once daily, or the co-administration of DRV/COBI (800 mg/150 mg) with F/TDF (200 mg/300 mg) in ART-naive patients. The primary efficacy end point of both studies was the proportion of patients with HIV-1 ribonucleic acid (RNA) < 50 copies/mL at week 24 (GS-US-299-0102) or week 48 (AMBER), as defined by the snapshot algorithm developed by the US FDA. In EMERALD (N = 1,141), patients with virologic suppression who had been treated with a stable ART consisting of a boosted PI (bPI) combined with F/TDF were randomized to D/C/F/TAF FDC once daily or continue their original regimen of bPI + F/TDF. The primary efficacy end point of this study was the proportion of patients with protocol-defined virologic rebound (HIV-1 RNA ≥ 50 copies/mL, as defined by the US FDA snapshot algorithm) through week 48 after the start of treatment. Overall, the recruited patients in the three studies had relatively mild disease and normal renal function. AMBER and EMERALD were still ongoing at the time of this review. There were no major methodological issues in the three studies, although there are challenges in interpretation of results, related to the handling of missing data and potential bias in the subgroup analysis. In addition, three phase I RCTs evaluated the bioequivalence and bioavailability of D/C/F/TAF relative to the administration of its individual components (COBI-boosted DRV plus F/TAF FDC) in healthy volunteers.

Bioequivalence

Results of the phase I RCTs suggested that the D/C/F/TAF 800 mg/150 mg/200 mg/10 mg FDC tablet is bioequivalent to combined administration of the separate drugs DRV, the FTC/TAF FDC, and COBI. Furthermore, single doses of the D/C/F/TAF FDC were well tolerated by healthy volunteers.

Efficacy

As shown in Table 1, findings from the RCTs demonstrated that D/C/F/TAF FDC was noninferior to co-administration of the individual components of DRV, COBI, and F/TDF for virologic success in treatment-naive patients, up to week 48 of the treatment. Moreover, switching to D/C/F/TAF FDC was noninferior to remaining on treatment with bPI + F/TDF for virologic rebound through 48 weeks in patients with virologic suppression.

Table 1: Virologic Response Rates Using the US FDA Snapshot Algorithm (HIV-1 RNA < 50 copies/mL)

	D/C/F/TAF	DRV + COBI + F/TDF[a]	D/C/F/TAF Versus Comparator	
			P Value	Difference in Percentage (95% CI)
GS-US-299-0102 (virologic success)				
FAS analysis set, n (%)	N = 103	N = 50		
HIV-1 RNA < 50 copies/mL at week 24	77 (74.8)	37 (74.0)	0.64[b]	3.3% (–11.4% to 18.1%)
HIV-1 RNA < 50 copies/mL at week 48	79 (76.7)	42 (84.0)	0.35[b]	–6.2% (–19.9% to 7.4%)
PP analysis set, n (%)	Week 24: N = 91 Week 48: N = 85	Week 24: N = 47 Week 48: N = 46		
HIV-1 RNA < 50 copies/mL at week 24	77 (84.6)	37 (78.7)	0.20[b]	8.3% (–5.3% to 22.0%)
HIV-1 RNA < 50 copies/mL at week 48	79 (92.9)	42 (91.3)	0.60[b]	2.4% (–8.8% to 13.7%)
AMBER (virologic success)				
ITT analysis set, n (%)	N = 362	N = 363		
IV-1 RNA < 50 copies/mL at week 48	331 (91.4)	321 (88.4)	< 0.0001[c]	2.7% (–1.6% to 7.1%)
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EMERALD (virologic rebound)				
ITT analysis set, n (%)	N = 763	N = 378		
HIV-1 RNA ≥ 50 copies/mL through week 48	19 (2.5)	8 (2.1)	< 0.001[d]	0.4% (–1.5% to 2.2%)
PP analysis set, n (%)	N = 721	N = 358		
HIV-1 RNA ≥ 50 copies/mL through week 48	14 (1.9)	3 (0.8)	< 0.001[d]	1.1% (–0.3 to 2.5)

C or COBI = cobicistat; CI = confidence interval; D or DRV = darunavir; FAS = full analysis set; F = emtricitabine; ITT = intention-to-treat; PP = per-protocol; RNA = ribonucleic acid; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[a] The comparator was bPI + F/TDF in the EMERALD study.

[b] *P* value for the superiority test comparing the percentage of virologic success between D/C/F/TAF and the control group.

[c] One-sided *P* value for noninferiority of D/C/F/TAF versus control (margin = 10%).

[d] One-sided *P* value for noninferiority of D/C/F/TAF versus control (margin = 4%).

Sources: Clinical Study Reports of GS-US-299-0102,[2] AMBER,[3] and EMERALD.[4]

Harms

Findings of the GS-US-299-0102 study showed that the risk of treatment-emergent adverse events (AEs) was similar between D/C/F/TAF FDC (92%) and COBI-boosted DRV + F/TDF FDC (94%) in treatment-naive patients. Serious AEs were infrequent, with 4.9% of patients in the D/C/F/TAF FDC group and 4% of patients in the control group reporting a serious AE during the study. An AE leading to premature study drug discontinuation was reported in 1.9% of patients in the D/C/F/TAF group and 4% in the control group. The most frequently reported AEs for D/C/F/TAF included diarrhea (21.4%), upper respiratory tract infection (15.5%), fatigue (13.6%), nausea (12.6%), and rash (11.7%). Patients in the control group

reported similar AEs. In terms of AEs specifically related to the treatment, patients in the D/C/F/TAF group showed a better renal safety profile and less decline in bone mineral density than those receiving DRV + COBI + F/TDF. According to the product monograph for D/C/F/TAF FDC,[5] however, the potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to administration of TAF cannot be excluded. The long-term bone health and future fracture risk are unknown, given the available data. The clinical expert consulted by CADTH expressed the concern about long-term use of TAF in adolescents because of its potential impact on bone development in this population.

Results of the two phase III ongoing RCTs (AMBER and EMERALD) also indicated that D/C/F/TAF FDC is well tolerated. They identified no new AEs beyond the known AEs associated with DRV/COBI FDC, bPI, and F/TDF FDC.

Potential Place in Therapy[1]

D/C/F/TAF FDC is the first PI-containing STR, and the seventh STR to become available on the Canadian market (preceded by Atripla, Complera, Odefsey, Stribild, Genvoya, and Triumeq).

PI-based therapies have fallen out of favour in preference to those incorporating integrase nuclear strand transfer inhibitors or non-nucleoside reverse transcriptase inhibitors, because of their need for pharmacologic boosting through cytochrome P450 inhibition, their side effects (diarrhea, worsening glucose intolerance, and dyslipidemia), and the lack of an STR formulation.

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 antiviral drugs 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. D/C/F/TAF FDC would offer another option for this patient group, but there is little to recommend it over the other options.

There is a need for an STR for patients with past treatment failures and genotypic viral resistance. Darunavir is likely the most active PI against PI-resistant virus. However, the dose used in D/C/F/TAF FDC is not the one recommended for treatment of resistant virus (600 mg, twice daily); therefore, D/C/F/TAF FDC does not fulfill this need.

Still, D/C/F/TAF FDC 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. It may be less desirable for patients with diabetes mellitus or dyslipidemia, because of its propensity to aggravate these, which should be easily identifiable by the prescriber. The potential for drug interactions would restrict its use somewhat or require alterations of concomitant therapy. It would most likely be used for patients with HIV already maintained on darunavir, either in the form of DRV/COBI or boosted by ritonavir. These patients are uncommon, as many would have been switched to an STR by now.

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

Cost

At the submitted daily price of $52.44 per tablet (taken once daily), D/C/F/TAF FDC is at parity with its individual components DRV/COBI ($23.87 daily) and F/TAF ($28.57 daily) and would therefore be cost-neutral. The submitted cost information for D/C/F/TAF did not include other available STRs as comparators, although they were noted as relevant comparators by the clinical expert consulted by CADTH. When compared with other STRs, D/C/F/TAF is more costly, with per person per year cost increases ranging from $1,614 (compared with elvitegravir/C/F/TDF) to $10,869 (compared with efavirenz/lamivudine/tenofovir disoproxil fumarate).

Conclusion

D/C/F/TAF FDC (Symtuza) is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with no known mutations associated with resistance to the individual components of D/C/F/TAF. The manufacturer's submission included a summary of three RCTs with a focus on the clinical efficacy and safety of D/C/F/TAF FDC in treatment-naive or treatment-experienced patients, and a summary of three bioequivalence/ bioavailability studies, which demonstrated that D/C/F/TAF FDC has a pharmacokinetic profile comparable to that of its individual components (COBI-boosted DRV and F/TAF FDC).

The efficacy data provided in the manufacturer's submission were derived from one completed phase II study and interim data from two phase III studies (AMBER and EMERALD). Virologic response (phase II study and AMBER) or virologic rebound (EMERALD) was the primary outcome measure in these studies. Study findings suggested that D/C/F/TAF FDC was noninferior to the co-administration of its individual components for virologic success in treatment-naive patients, at week 24 (phase II study) and week 48 (AMBER). In patients with virologic suppression as a result of prior ART with boosted PI + F/TDF, switching to D/C/F/TAF FDC was noninferior to remaining on previous ART for virologic rebound, at week 48 (EMERALD).

D/C/F/TAF FDC has similar safety profile to the co-administration of DRV + COBI + F/TDF FDC, or bPI + F/TDF FDC in the included studies. In general, D/C/F/TAF FDC is well tolerated. The studies identified no new safety signals beyond the known adverse drug reactions related to DRV + COBI + F/TDF FDC, DRV/COBI FDC, or bPI + F/TDF FDC.

1. Product Information

1.1 Health Canada–Approved Indications

A complete regimen for the treatment of HIV type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with no known mutations associated with resistance to the individual components of Symtuza.

1.2 Requested Listing Criteria

Requested Listing Criteria
Treatment of HIV-1 infection in adults and adolescents with no known mutations associated with resistance to the individual components of Symtuza.

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

This report contains references provided by the manufacturer as well as by CADTH. Square brackets have been placed around CADTH's references for the purpose of distinguishing the sources of these references.

1.3.1 Rationale

HIV is a chronic condition that can be managed through treatment with antiretroviral therapy (ART). ART does not provide a cure because of the persistence of latent viral reservoirs. Therefore, current goals of treatment are to suppress viral replication to prevent disease progression, HIV-related morbidity, and mortality; to restore or preserve immunologic function; and to prevent onward transmission of the virus.

Early ART regimens were associated with high pill burdens and/or complex administration protocols, but ART-related pill burden has decreased over time.[1] However, aging of the prevalent HIV population means increased pill burden for the treatment of comorbid conditions that become more common with age (e.g., hypertension, type 2 diabetes, and dyslipidemia). ART may form only a small component of the overall pill burden in people living with HIV. It has been shown that the longer duration of ART and more than three comorbidities are associated with a significant increase in pill burden.[2]

Since ART is not curative and must be taken indefinitely to maintain virologic suppression, adherence to ART is important. It is estimated that 95% or greater adherence to ART is required for maximum efficacy.[3] Poor adherence leads to subtherapeutic dosage and is also the leading cause of treatment failure.[4] Several studies have linked high pill burdens and complex administration regimens to lower adherence; therefore, any strategies that simplify administration and/or minimize pill burden, such as single-tablet regimens (STRs) containing fixed-dose combinations (FDCs), may lead to better adherence to ART in people living with HIV.[5] Studies have shown that STRs are associated with significantly better adherence than multiple-tablet regimens (MTRs) and that adherence is significantly better with once daily versus twice daily administration.[6-9]

A few real-world studies have directly compared the effectiveness of STRs and MTRs in routine clinical practice. A recent large-scale (N > 15,000 patients) US-based study

compared clinical outcomes in veterans (97% male, mean age 52 years, 40% with history of drug or substance abuse) treated with either any STR or any MTR over the period 2006 to 2012.[10] During follow-up, a significantly higher proportion of STR-treated patients achieved undetectable viral load compared with those treated with MTRs (63.9% versus 59.6%; $P < 0.001$). After adjustment for baseline covariates, STR-treated patients had a 31% lower odds of hospitalization than MTR-treated patients.[9, 10]

Symtuza contains four components (darunavir, cobicistat, emtricitabine, tenofovir alafenamide [D/C/F/TAF]), each of which has been extensively characterized in clinical trials. Darunavir (D or DRV, 800 mg) is a protease inhibitor (PI) that is administered in combination with a pharmaco-enhancing drug such as cobicistat (C or COBI, 150 mg). DRV inhibits the cleavage of the gag-pol polyprotein, thereby blocking production of the mature HIV-1 protease. A key advantage of DRV is its high genetic barrier (multiple mutations are required to confer resistance) relative to both the non-nucleotide/nucleoside reverse transcriptase inhibitors (NNRTIs) and some of the integrase inhibitors, which makes it a preferred option for people with a history of poor compliance. Therefore, patients who fail PI-based treatment seldom develop antiviral resistance. Symtuza contains the pharmaco-enhancing drug COBI, which demonstrates more specific activity against cytochrome P450 3A4 than ritonavir, thereby reducing the potential for drug–drug interactions with some concomitantly administered drugs. COBI has no antiviral activity; therefore, there is no possibility for the development of resistance against COBI. DRV/COBI is commercially available as Prezcobix (DRV/COBI, 800 mg/150 mg) tablets.[11]

In addition, emtricitabine (F or FTC 200 mg) is a nucleoside reverse transcriptase inhibitor (NRTI) indicated in combination with other drugs for the treatment of HIV-1. It inhibits HIV-1 reverse transcriptase by acting as a competitive inhibitor for deoxycytidine 5′-triphosphate, and incorporation of FTC into nascent viral nucleic acid causes chain termination, thereby interfering with the production of new viral particles at the transcription level. Tenofovir alafenamide (TAF, 10 mg) is a prodrug of the nucleotide reverse transcriptase inhibitor tenofovir (TFV). TAF offers an improved renal and bone safety profile compared with tenofovir disoproxil fumarate (TDF), owing to its distinct metabolism and improved intracellular delivery of TFV (and tenofovir diphosphate), thereby reducing TFV plasma concentrations. FTC/TAF is commercially available as Descovy (FTC/TAF, 200 mg/10 mg) tablets.[12]

Together, this D/C/F/TAF STR simplifies and substantially reduces the pill burden associated with ART, which is, in turn, associated with improved adherence compared with MTRs and/or twice-daily administration. Therefore, it is more convenient for people living with HIV. Discontinuation rates in patients switching to STRs are low. Real-world studies have shown better effectiveness with STRs than with MTRs in terms of virologic suppression rates and hospitalization rates.[9, 10]

A Notice of Compliance for Symtuza (D/C/F/TAF), as a complete regimen for the treatment of HIV-1 infection in adults and adolescents with no known mutations associated with resistance to the individual components of D/C/F/TAF, was granted by Health Canada on March 8, 2018.[1]

1.3.2 Place in Therapy

Symtuza is the first PI-containing once daily STR. The expected place in therapy for Symtuza is in the treatment of HIV-1 infection, including initial therapy, in adults and

adolescents (aged 12 years and older with body weight at least 40 kg) without known mutations associated with resistance to the individual components of Symtuza.

Canadian and international guidelines recommend an initial ART with two NRTIs, plus a third active drug from a different class.[4, 13-17]

FTC plus TAF is the recommended NRTI backbone, and it is available as Descovy,[14] an FDC tablet available as either F/TAF 200 mg/10 mg or F/TAF 200 mg/25 mg, to be taken once daily with or without food. When used in combination with an ART requiring a pharmacokinetic (PK) enhancer, including boosted DRV, the recommended dose of F/TAF is 200 mg/10 mg. Descovy received a CADTH Canadian Drug Expert Committee (CDEC) recommendation for use in combination with other ARTs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adult and pediatric patients aged 12 years and older (weighing at least 35 kg).[18]

DRV has proven efficacy in both treatment-naive and highly treatment-experienced people living with HIV; for those with a high genetic barrier, it is regarded as the first choice PI. COBI, a pharmacological booster without inherent anti-HIV activity, is available as a co-formulation with DRV in Prezcobix.[16] Prezcobix is commercially available and contains DRV and COBI (800 mg/150 mg); it is taken once daily with food. It received a CDEC recommendation for the treatment of HIV infection in treatment-naive and treatment-experienced patients without DRV resistance-associated mutations.[19]

Symtuza contains the most commonly prescribed doses of the individual components (D/C/F/TAF; 800 mg/150 mg/200 mg/10 mg).

1.3.3 Dosage Considerations

This FDC STR is available in one strength for the proposed indication: D/C/F/TAF (800 mg/150 mg/200 mg/10 mg). The 800 mg dose of DRV is approved for treatment-naive patients and treatment-experienced patients with no DRV resistance-associated mutations. COBI 150 mg has been shown to boost DRV levels similarly to 100 mg ritonavir, and Prezcobix contains DRV/COBI (800 mg/150 mg). FTC 200 mg is the marketed dose, and TAF is available in 10 mg or 25 mg. TAF 10 mg was selected based on the results of the phase I study.[20] As recommended in the Descovy product monograph, the FTC/TAF dose (200 mg/10 mg) is recommended when Descovy is used in combination with DRV + COBI.[12] Dose titration is not required.

2. Clinical Evidence

For Symtuza (D/C/F/TAF), the efficacy, resistance, and safety profile is derived from the DRV/COBI and F/TAF development programs, supported by the phase II double-blind study GS-US-299-0102, the only phase II clinical study included in the new drug submission (NDS) to Health Canada on 12 March 2017.

Due to contractual limitations, Janssen is unable to summarize or reference specific Gilead studies contained in previous Health Canada files for Genvoya and Descovy (F/TAF). After consulting with CADTH, Janssen included one comprehensive clinical summary referencing publicly available information for the Gilead F/TAF studies. In addition, two new Janssen phase III studies (AMBER – TMC114FD2HTX3001; EMERALD – TMC114IFD3013) that were not included in the NDS were summarized in this template. The 48-week data from these studies became available only after the submission of the NDS in March 2017. These two pivotal studies were included in the new drug application and submitted to the US FDA on September 26, 2017.

Key results from the phase II study GS-US-299-0102 and the two phase III studies AMBER (TMC114FD2HTX3001) and EMERALD (TMC114IFD3013) are summarized in Section 2.1.

2.1 Pivotal Clinical Studies

Table 2: Summary of the Pivotal Clinical Studies for Symtuza (D/C/F/TAF)

Study Name	Design	Objectives	Population
GS-US-299-0102[21] (completed) Included in the NDS for Health Canada review	Phase II, randomized, double-blind, multi-centre, active-controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC versus DRV + COBI + F/TDF	**Primary objective** • To evaluate the efficacy of a regimen containing D/C/F/TAF versus DRV + COBI + F/TDF in ART-naive adult patients living with HIV-1, as determined by the achievement of HIV-1 RNA < 50 copies/mL at week 24	ART-naive, adult patients
AMBER TMC114FD2HTX3001[24] (ongoing) Not included in the NDS	Phase III, randomized, active-controlled, double-blind study to evaluate efficacy and safety of D/C/F/TAF FDC versus DRV/COBI + F/TDF	**Primary objective** • To demonstrate noninferiority in efficacy of a D/C/F/TAF FDC tablet versus DRV/COBI FDC co-administered with F/TDF FDC in ART treatment-naive adult patients living with HIV-1, as determined by the proportion of virologic responders, defined as HIV-1 RNA < 50 copies/mL at week 48 (FDA snapshot approach), with a maximum allowable difference of 10%	ART-naive, adult patients

Study Name	Design	Objectives	Population
EMERALD TMC114IFD3013[25] (ongoing) Not included in the NDS	Phase III, randomized, active-controlled, open-label study to evaluate the efficacy, safety, and tolerability of switching to D/C/F/TAF FDC versus continuing the current boosted PI combined with F/TDF	**Primary objective** • To demonstrate noninferiority in efficacy of D/C/F/TAF FDC STR relative to continuing the current bPI combined with F/TDF in patients with virologic suppression of HIV infection, with regard to the proportion of virologic rebounders through week 48, with a maximum allowable difference of 4%	ART-experienced, adult patients with virologic suppression

ART = antiretroviral therapy; bPI = boosted protease inhibitor; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; FDC = fixed-dose combination; F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada); NDS = new drug submission; RNA = ribonucleic acid; STR = single-tablet regimen; TDF = tenofovir disoproxil fumarate.

2.1.1 GS-US-299-0102 (In the NDS for Health Canada Review)

a) Study Characteristics

GS-US-299-0102 was a phase II double-blind randomized controlled trial (RCT) in ART-naive patients with HIV-1 infection, involving D/C/F/TAF and DRV + COBI + F/TDF and thus allowing a direct comparison of the safety and efficacy of TAF versus TDF in the context of treatment with COBI-boosted DRV.

Table 3: Summary of Study Characteristics for GS-US-299-0102[21, 23]

Characteristics		Details for GS-US-299-0102
Study Design	**Objective**	Pivotal efficacy and safety study
	Blinding	Double-blind
	Study period	April 2012 to February 2014
	Study centres	38 study centres: 37 centres in the US and 1 centre in Puerto Rico
	Design	Noninferiority
Study Population	**Randomized (N)**	153
	Inclusion criteria	• Adult (> 18 years) men or nonpregnant women • General medical condition, in the investigator's opinion, that would not interfere with the assessments and the completion of the trial • Plasma HIV-1 RNA levels ≥ 5,000 copies/mL • CD4+ cell count > 50 cells/μL • Treatment-naive: no prior use of any approved or experimental anti-HIV drug for any length of time • Screening genotype report provided by Gilead Sciences showed sensitivity to DRV, TDF, and FTC • Normal ECG (or, if abnormal, determined by the investigator to be not clinically significant) • Adequate renal function: estimated glomerular filtration rate (eGFR) ≥ 70 mL/min according to the Cockcroft–Gault formula
	Exclusion criteria	• A new AIDS-defining condition diagnosed within the 30 days prior to screening • Hepatitis B surface antigen (HBsAg)–positive • Hepatitis C antibody–positive • Proven acute hepatitis in the 30 days prior to study entry • History of or experiencing decompensated cirrhosis
Drugs	**Intervention**	D/C/F/TAF (800 mg/150 mg/200 mg/10 mg) once daily with food

Characteristics		Details for GS-US-299-0102
	Comparator(s)	DRV 800 mg + COBI 150 mg tablet + F/TDF (200 mg/300 mg) FDC once daily with food
Duration	**Run-in**	Not applicable
	Treatment	48 weeks
	Follow-up	After week 48, patients continued to take blinded study drug and attend visits every 12 weeks until treatment assignments were unblinded, at which point all patients returned for an unblinding visit; participation in the open-label extension phase of GS-US-292-0102 was optional.
Outcomes	**Primary End Point(s)**	Virologic success, week 24
	Other End Points	Virologic success, week 48 HIV-1 RNA CD4+ count
Notes	**Publications**	Mills A, Crofoot G, Jr., McDonald C, Shalit P, Flamm JA, Gathe J, Jr., et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study. Journal of acquired immune deficiency syndromes. 2015;69(4):439-45. PubMed PMID: 25867913. NCT01565850

COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FDC = fixed-dose combination; FTC = emtricitabine; F/TDF = emtricitabine/tenofovir disoproxil fumarate; TDF = tenofovir disoproxil fumarate; RNA = ribonucleic acid.

Intervention and Comparators

Patients were randomized in a 2:1 ratio to one of the following two treatment arms:

- Treatment arm 1: FDC tablet of DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg + placebos to match DRV 800 mg (400 mg tablet × 2) and COBI 150 mg tablet and FDC tablet FTC 200 mg/TDF 300 mg once daily (five tablets in total)
- Treatment arm 2: DRV 800 mg (400 mg tablet × 2) + COBI 150 mg tablet + FDC tablet FTC 200 mg/TDF 300 mg + placebos to match an FDC tablet of DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg once daily (five tablets in total).

No concomitant medications were required. Any medications different from the investigational medication had to be recorded.

Outcomes

The primary efficacy end point is the percentage of patients who achieved HIV-1 ribonucleic acid (RNA) < 50 copies/mL at week 24, as defined by the FDA snapshot analysis algorithm. Secondary efficacy end points included the percentage of patients with HIV-1 RNA < 50 copies/mL at week 48 as defined by the snapshot analysis algorithm, the change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell count at weeks 24 and 48.

The PKs of TAF, TFV, DRV, COBI, and FTC was assessed for all patients who participated in an intensive PK substudy. PK parameters estimated in the substudy included maximum plasma concentration (C_{max}), time at which maximum concentration is observed (t_{max}), concentration over the 24-hour dosage interval (C_{tau}), area under the plasma concentration-time curve over the dosage interval (AUC_{tau}), and half-life (t½).

Safety end points were adverse events (AEs) and clinical laboratory tests, including bone mineral density (BMD), serum creatinine, and renal biomarkers to evaluate the safety and tolerability of the treatment regimens.

Statistical Analyses

The purpose of the primary efficacy end point was to assess the noninferiority of treatment with D/C/F/TAF relative to treatment with DRV + COBI + F/TDF. Noninferiority was assessed using a conventional 95% confidence interval (CI) approach, with a noninferiority margin of 12%. Noninferiority was concluded if the lower bound of the two-sided 95% CI of the difference (D/C/F/TAF – DRV + COBI + F/TDF) in the response rate was more than –12%. A total sample size of 150 patients (100 in the D/C/F/TAF group) had 56% power to evaluate noninferiority with respect to the response rate of HIV-1 RNA < 50 copies/mL at week 24 if a response rate of 88% for both groups and a noninferiority margin of 0.12 were assumed.

The differences in changes from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count between treatment groups and the associated 95% CI were constructed using analysis of variance model including baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) and race (black or nonblack) as fixed effects in the model. The primary analysis used a full analysis set (FAS) and a per-protocol (PP) analysis set. The analyses for all the secondary efficacy end points were conducted using the FAS, and the end point related to the virologic response at week 48 was also analyzed using the PP analysis set. The FAS included all patients who were randomized into the study and received at least one dose of study drug. The PP analysis set included all patients who were randomized into the study, received at least one dose of study drug, and did not commit any major protocol violation, including violation of key entry criteria. The safety analysis set was the primary analysis set for safety analyses and included all patients who were randomized into the study and received at least one dose of study drug. Alpha level of 0.05 was used to construct the 95% CIs.

Alpha level was not adjusted in this study, because the primary efficacy evaluation was exploratory in nature. Missing values of virologic outcomes were treated either as failure (HIV-1 RNA ≥ 50 copies/mL) or excluded (observed data) from analysis.

b) Results

Baseline Characteristics

General baseline characteristics were similar between the two treatment groups.

Table 4: Summary of Baseline Characteristics for Study GS-US-299-0102[23]

Characteristic	D/C/F/TAF (N = 103)	DRV + COBI + F/TDF (N = 50)	Total (N = 153)	D/C/F/TAF Versus DRV + COBI + F/TDF (*P* value)
Age (years)				
N	103	50	153	0.23
Mean (SD)	35 (11.3)	37 (10.9)	35 (11.2)	
Median	31	36	33	
Q1 to Q3	25 to 42	28 to 44	26 to 43	
Min to max	20 to 68	18 to 57	18 to 68	
Sex, n (%)				
Male	95 (92.2)	47 (94.0)	142 (92.8)	0.69
Female	8 (7.8)	3 (6.0)	11 (7.2)	
Race, n (%)				
White	62 (60.2)	30 (60.0)	92 (60.1)	0.99
Black or African American	36 (35.0)	17 (34.0)	53 (34.6)	

Characteristic	D/C/F/TAF (N = 103)	DRV + COBI + F/TDF (N = 50)	Total (N = 153)	D/C/F/TAF Versus DRV + COBI + F/TDF (*P* value)
Asian	2 (1.9)	1 (2.0)	3 (2.0)	
Native Hawaiian or other Pacific Islander	1 (1.0)	1 (2.0)	2 (1.3)	
Other	2 (1.9)	1 (2.0)	3 (2.0)	
Ethnicity, n (%)				
Hispanic or Latino	23 (22.3)	9 (18.0)	32 (20.9)	0.54
Not Hispanic or Latino	80 (77.7)	41 (82.0)	121 (79.1)	
Baseline body mass index (kg/m^2)				
N	103	50	153	0.94
Mean (SD)	26.3 (4.97)	26.1 (4.53)	26.2 (4.81)	
Median	25.1	24.7	24.9	
Q1 to Q3	22.4 to 29.6	22.7 to 29.0	22.7 to 29.2	
Min to max	18.2 to 42.7	17.6 to 37.9	17.6 to 42.7	
HIV-1 RNA (log_{10} copies/mL)				
N	103	50	153	0.39
Mean (SD)	4.70 (0.516)	4.65 (0.514)	4.68 (0.515)	
Median	4.67	4.58	4.66	
Q1 to Q3	4.43 to 4.93	4.28 to 4.91	4.37 to 4.91	
Min to max	3.27 to 6.12	3.59 to 6.29	3.27 to 6.29	
CD4 cell count (cell/µL)				
N	103	50	153	0.14
Mean (SD)	395 (169.3)	464 (261.6)	417 (205.7)	
Median	368	433	384	
Q1 to Q3	270 to 515	320 to 606	283 to 532	
Min to max	7 to 909	49 to 1,463	7 to 1,463	
HIV disease status				
Asymptomatic	93 (90.3)	44 (88.0)	137 (89.5)	0.39
Symptomatic HIV infections	8 (7.8)	3 (6.0)	11 (7.2)	
AIDS	2 (1.9)	3 (6.0)	5 (3.3)	
$eGFR_{CG}$ (mL/min)				
N	103	50	153	0.17
Mean (SD)	119.6 (26.89)	115.7 (31.41)	118.3 (28.40)	
Median	116.0	109.6	114.6	
Q1 to Q3	97.0 to 137.6	92.5 to 131.4	96.5 to 132.3	
Min to max	77.3 to 223.0	73.7 to 259.2	73.7 to 259.2	

COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; $eGFR_{CG}$ = estimated glomerular filtration rate calculated using the Cockcroft–Gault method; F/TDF = emtricitabine/tenofovir disoproxil fumarate; Q = quartile; SD = standard deviation.

Patient Disposition

Of the 232 patients screened, 153 were randomized and received at least one dose of study drug (D/C/F/TAF 103 patients; DRV + COBI + F/TDF 50 patients). Patients were randomized at 40 sites in two countries.[23] Among those discontinued from the treatment, no patients withdrew due to lack of efficacy, protocol violation, or death.

Table 5: Summary of Patient Disposition for GS-US-299-0102[23]

Disposition	GS-US-299-0102	
	D/C/F/TAF	DRV + COBI + F/TDF
Screened	232	
Randomized, N	103	50
Discontinued, N (%)[a]	19 (18.4)	8 (16.0)
WDAEs	1 (1.0)	2 (4.0)
Lost to follow-up	10 (9.7)	4 (8.0)
Investigator's discretion	2 (2.0)	0
Withdrew consent	4 (4.0)	2 (4.0)
Patient non-compliance	2 (2.0)	0
Full analysis set,[b] **N**	103	50
Per-protocol set in week 24, N (%)	91 (88)	47 (94)
Per-protocol set in week 48, N (%)	85 (83)	46 (92)
Safety, N	103	50

WDAE = withdrawal due to adverse event.

[a] Patients prematurely discontinuing study drug could still be in the study (i.e., not prematurely discontinued from the study).

[b] Full analysis set was the primary analysis set for efficacy analyses and included all patients who (1) were randomized into the study and (2) received one or more dose of study medication. All efficacy data including data collected after the last dose of study drug was included, unless specified otherwise.

Efficacy

Virologic outcomes at week 24 were similar between the two treatment groups for the primary end point analysis for the FAS. Virologic success rates were as follows: D/C/F/TAF 74.8%, DRV + COBI + F/TDF 74.0% (difference in percentage 3.3%; 95% CI, –11.4% to 18.1%. Because the lower bound of the two-sided 95% CI of the difference in the response rate (D/C/F/TAF – DRV + COBI + F/TDF) was greater than the pre-specified –12% noninferiority margin, D/C/F/TAF was determined to be noninferior to DRV + COBI + F/TDF. Virologic success rates at week 24 were similar between treatment groups using the week 24 PP analysis set, as follows: D/C/F/TAF 84.6%, 77 of 91 patients; DRV + COBI + F/TDF 78.7%, 37 of 47 patients (difference in percentage 8.3%; 95% CI, –5.3% to 22.0%; Table 6).

The rates of virologic success through week 48, assessed using the FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) using the FAS, were as follows: D/C/F/TAF 76.7%, DRV + COBI + F/TDF 84.0% (difference in percentage –6.2%; 95% CI, –19.9% to 7.4%). The difference in rates of virologic success between treatment arms was primarily due to a difference in the numbers of patients who discontinued study drug for other reasons and whose last available HIV-1 RNA result was ≥ 50 copies/mL (D/C/F/TAF 8.7%, nine patients; DRV + COBI + F/TDF 4.0%, two patients). Virologic success rates for the week 48 PP analysis set were similar between the two treatment groups, as follows: D/C/F/TAF 92.9%, 79 of 85 patients, DRV + COBI + F/TDF 91.3%, 42 of 46 patients (difference in percentage 2.4%; 95% CI, –8.8% to 13.7%).

The mean increases from baseline in CD4 cell count were similar for each treatment group through week 48 (observed data), as follows: D/C/F/TAF 231 (standard deviation [SD] 141.9) cells/μL; DRV + COBI + F/TDF 212 (SD 151.5) cells/μL.

The median adherence rate to active study drug was similar in the D/C/F/TAF (98.8%) and DRV + COBI + F/TAF (98.2%) groups.

Table 6: GS-US-299-0102 — Virologic Success Rates Using the US FDA Snapshot Algorithm HIV-1 RNA < 50 copies/mL

	D/C/F/TAF	DRV + COBI + F/TDF	D/C/F/TAF Versus DRV + COBI + F/TDF	
			P Value[a]	Difference in Percentage (95% CI)
FAS analysis set, n (%)	N = 103	N = 50		
HIV-1 RNA < 50 copies/mL at week 24	77 (74.8)	37 (74.0)	0.64	3.3 (–11.4 to 18.1)
HIV-1 RNA < 50 copies/mL at week 48	79 (76.7)	42 (84.0)	0.35	–6.2 (–19.9 to 7.4)
PP analysis set, n (%)	Week 24: N = 91 Week 48: N = 85	Week 24: N = 47 Week 48: N = 46		
HIV-1 RNA < 50 copies/mL at week 24	77 (84.6)	37 (78.7)	0.20	8.3 (–5.3 to 22.0)
HIV-1 RNA < 50 copies/mL at week 48	79 (92.9)	42 (91.3)	0.60	2.4 (–8.8 to 13.7)

CI = confidence interval; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; FAS = full analysis set; F/TDF = emtricitabine/tenofovir disoproxil fumarate; PP = per-protocol; RNA = ribonucleic acid; TAF = tenofovir alafenamide.

[a] *P* value for the superiority test comparing the percentage of virologic success between D/C/F/TAF and the control group was from the Cochran–Mantel–Haenszel test stratified by baseline HIV-1 RNA and race strata.

Source: Clinical Study Report for GS-US-299-0102.[2]

2.1.2 TMC114FD2HTX3001 (Not Submitted to Health Canada Due to Data Availability After NDS Filing)

a) Study Characteristics

TMC114FD2HTX3001 (AMBER) is an ongoing, active-controlled, double-blind, phase III RCT in ART-naive patients with HIV-1 infection who received either (1) D/C/F/TAF FDC or (2) DRV/COBI FDC co-administered with F/TDF FDC.

Table 7: Summary of Study Characteristics for TMC114FD2HTX3001[24]

Characteristics		Details for TMC114FD2HTX3001 (AMBER)
Study Design	**Objective**	Pivotal efficacy and safety study
	Blinding	Double-blind
	Study period	July 2015 to March 2017
	Study centres	121 study centres: Belgium (4), Canada (5), France (12), Germany (12), Italy (10), Poland (7), Russia (11), Spain (20), UK (7), US (33)
	Design	Noninferiority
Study Population	**Randomized (N)**	725
	Inclusion criteria	• ART-naive (never treated with an ART including pre-exposure or post-exposure prophylaxis); no prior use of any approved or experimental anti-HIV drug for any length of time • Screening plasma HIV-1 RNA level ≥ 1,000 copies/mL • CD4+ cell count > 50 cells/mm^3 • Screening HIV-1 genotype report had to show full sensitivity to DRV, TDF, and FTC • Screening $eGFR_{CG}$ ≥ 70 mL/min
	Exclusion criteria	• Had been diagnosed with a new AIDS-defining condition within 30 days prior to screening • Had proven or suspected acute hepatitis within 30 days prior to screening • Were hepatitis C antibody–positive • Were hepatitis B surface antigen–positive • Had a history of cirrhosis

Characteristics		Details for TMC114FD2HTX3001 (AMBER)
Drugs	**Intervention**	Single D/C/F/TAF (800 mg/150 mg/200 mg/10 mg) FDC tablet once daily
	Comparator(s)	DRV/COBI (800 mg/150 mg) FDC co-administered with F/TDF (200 mg/300 mg) FDC once daily
Duration	**Run-in**	Not applicable
	Treatment	48 weeks
	Follow-up	After week 48, patients continued to take blinded study drug and attend visits every 12 weeks until treatment assignments were unblinded. Then patients received D/C/F/TAF during a single-group treatment phase up to week 96 (ongoing).
Outcomes	**Primary end point(s)**	Virologic success, week 48
	Other end points	HIV-1 RNA, week 48 CD4+ count, week 48 Resistance-associated mutations at screening Safety
Notes	**Publications**	Not applicable. NCT02431247

ART = antiretroviral therapy; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; $eGFR_{CG}$ = estimated glomerular filtration rate calculated using the Cockcroft–Gault method; FDC = fixed-dose combination; FTC = emtricitabine; F/TDF = emtricitabine/tenofovir disoproxil fumarate; TDF = tenofovir disoproxil fumarate.

Intervention and Comparators

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

- Treatment arm 1 (test): single D/C/F/TAF (800 mg/150 mg/200 mg/10 mg) FDC tablet once daily + DRV/COBI FDC–matching and F/TDF FDC–matching placebo tablets once daily
- Treatment arm 2 (control): DRV/COBI (800 mg/150 mg) FDC co-administered with F/TDF (200 mg/300 mg) FDC once daily + D/C/F/TAF FDC–matching placebo tablet once daily.

Outcomes

The primary efficacy end point was the proportion of patients who have HIV-1 RNA < 50 copies/mL at week 48, as defined by the FDA snapshot approach.

Safety was evaluated based on AEs and results of clinical laboratory tests (hematology, urine chemistry, serum chemistry, urinalysis, urine renal biomarkers, serum cystatin C, metabolic panel, pregnancy testing, hepatitis testing, and bone biomarkers).

Based on the individual plasma concentration-time data, PK parameters were derived using population pharmacokinetic modelling and Bayesian feedback: 1) trough (predose) plasma concentration and area under the plasma concentration-time curve over the 24-hour dosage interval (AUC_{24h}) for DRV; 2) plasma concentrations two hours after administration and AUC_{tau} for TAF. (Note that AUC_{tau} and AUC_{24h} have the same meaning, as the dosage interval is 24 hours for all analytes.)

Statistical Analyses

A sample size of 670 patients (335 in each group) was able to provide 90% power, assuming a virologic response rate of 80% in both treatment groups and a significance level of 0.025 for the one-sided test. The primary analysis consisted of a noninferiority evaluation of the D/C/F/TAF FDC tablet (investigational treatment group) versus DRV/COBI FDC co-

administered with F/TDF FDC (control group), with respect to the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 after the start of treatment in this study (as defined by the FDA snapshot approach). It was to be concluded that the D/C/F/TAF FDC tablet is not inferior to the control regimen if the lower bound of the two-sided 95% CI of the difference in response rate between treatment groups (D/C/F/TAF group versus control group) was greater than –10% (i.e., a margin of 10% is applied to noninferiority assessment). The difference (with associated 95% CI) was constructed using the stratum-adjusted Mantel–Haenszel (MH) difference in proportions, where the re-classified stratification factors (HIV-1 RNA level [≤ 100,000 copies/mL or > 100,000 copies/mL] and CD4+ cell count [< 200 cells/mm^3 or ≥ 200 cells/mm^3]) determined the strata.

As secondary analyses, the proportion of patients with HIV-1 RNA < 20 copies/mL and < 200 copies/mL at week 48, as defined by the FDA snapshot approach, was analyzed using the same method as the primary efficacy end point to compare treatment groups.

The intention-to-treat (ITT) analysis set included all patients who were randomized and received at least one dose of treatment, [redacted] All other efficacy end points were assessed in the ITT analysis set.

Missing HIV-1 RNA data were imputed with the patient's baseline value or using the last observation carried forward approach.

b) Results

Baseline Characteristics

There were 32 patients (4.4%) recruited from Canada. No relevant differences in demographic and baseline characteristics were observed between the treatment groups.

Table 8: Summary of Baseline Characteristics for TMC114FD2HTX3001 (AMBER)[24]

Characteristic	D/C/F/TAF	DRV + COBI + F/TDF	Total
Analysis set: ITT, N	**362**	**363**	**725**
Age at screening (years)			
[redacted]	[redacted]	[redacted]	[redacted]
Median (min to max)	34.0 (19 to 61)	34.0 (18 to 71)	34.0 (18 to 71)
[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]
Gender, n (%)			
Female	44 (12.2)	41 (11.3)	85 (11.7)
Male	318 (87.8)	322 (88.7)	640 (88.3)

Characteristic	D/C/F/TAF	DRV + COBI + F/TDF	Total
Race, n (%)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
N	360	361	721
White	300 (82.9)	300 (82.6)	600 (82.8)
Black or African American	40 (11.1)	40 (11.1)	80 (11.1)
Other	20 (5.5)	21 (5.8)	41 (5.7)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
HIV-1 viral load at baseline, n (%)			
N	362	363	725
[redacted]	[redacted]	[redacted]	[redacted]
Log_{10} Median (min to max)	4.4385 (1.279 to 6.632)	4.5682 (2.994 to 6.681)	4.5172 (1.279 to 6.681)
≥ 100,000 copies/mL	60 (16.6)	70 (19.3)	130 (17.9)
< 100,000 copies/mL	302 (83.4)	293 (80.7)	595 (82.1)
CD4+ (cells/mm^3), n (%)			
N	362	363	725
[redacted]	[redacted]	[redacted]	[redacted]
Median (min to max)	461.5 (46 to 1454)	440.0 (38 to 1,456)	453.0 (38 to 1,456)
< 200 cells/mm^3	22 (6.1)	29 (8.0)	51 (7.0)
≥ 200 cells/mm^3	340 (93.9)	334 (92.0)	674 (93.0)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
$eGFR_{CG}$ (mL/min)			
N	362	363	725
[redacted]	[redacted]	[redacted]	[redacted]
Median (min to max)	119.3 (74 to 257)	118.4 (57 to 207)	119.1 (57 to 257)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; $eGFR_{CG}$ = estimated glomerular filtration rate calculated using the Cockcroft–Gault method; F/TDF = emtricitabine/tenofovir disoproxil fumarate.

Patient Disposition

In total, 725 of the 866 screened patients were enrolled in the study. The screening failure rate was 16.3%. The majority of patients were still ongoing in the study at the time of the week 48 visit (93.6% and 92.3% in the D/C/F/TAF and control group, respectively). Discontinuation rates up to week 48 were similar in both treatment groups.

Table 9: Summary of Patient Disposition for TMC114FD2HTX3001 (AMBER)[24]

Disposition	TMC114FD2HTX3001	
	D/C/F/TAF	DRV + COBI + F/TDF
Screened	866	
Randomized, N	362	363
Discontinued, N (%)[a]	23 (6.4)	28 (7.7)
Death	0	1 (0.3)
WDAEs	8 (2.2)	15 (4.1)
Lost to follow-up	5 (1.4)	5 (1.4)
Patient non-compliance	1 (0.3)	0
Physician decision	3 (0.8)	0
Withdrew consent	4 (1.1)	6 (1.7)
Other	2 (0.6)	1 (0.3)
Intention-to-treat (ITT), N	362	363
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; eGFRCG; F/TDF = emtricitabine/tenofovir disoproxil fumarate. WDAE = withdrawal due to adverse event.

[a] Patients prematurely discontinuing study treatment prior to the data cut-off date.

Efficacy

At week 48, the virologic response rate (HIV-1 RNA < 50 copies/mL; FDA snapshot approach; primary end point) was similar in both treatment groups: 91.4% (331/362) in the D/C/F/TAF group versus 88.4% (321/363) in the control group. D/C/F/TAF was noninferior to the control (i.e., lower limit of the stratified MH 95% CI around the difference between D/C/F/TAF and control was above the protocol-defined noninferiority margin of –10%) with a treatment difference in virologic response between D/C/F/TAF and control of 2.7% (95% CI, –1.6 to 7.1) and a corresponding one-sided noninferiority $P < 0.001$. The virologic rebound rate was low in each treatment group: 4.4% (16/362) in the D/C/F/TAF group versus 3.3% (12/363) in the control group.

[redacted]

[redacted]

The median adherence rate was 100% in both treatment groups.

Table 10: TMC114FD2HTX3001 (AMBER) — Virologic Success Rates Using the US FDA Snapshot Algorithm HIV-1 RNA < 50 copies/mL

	D/C/F/TAF	DRV + COBI + F/TDF	D/C/F/TAF Versus DRV + COBI + F/TDF	
			P Value[a]	Difference in Percentage (95% CI)[b]
ITT analysis set, n (%)	N = 362	N = 363		
HIV-1 RNA < 50 copies/mL at week 48	331 (91.4)	321 (88.4)	< 0.0001	2.7 (–1.6 to 7.1)
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; COBI = cobicistat; D or DRV = darunavir; F = emtricitabine; ITT = intention-to-treat; PP = per-protocol; RNA = ribonucleic acid; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[a] One-sided *P* value for noninferiority of D/C/F/TAF versus control (margin = 10%).

[b] Based on stratum-adjusted MH test, where stratification factors are HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) and CD4+ cell count (< 200 cells/µL or ≥ 200 cells/µL).

Source: Clinical Study Report for AMBER.[3]

2.1.3 TMC114IFD3013 (Not Submitted to Health Canada Due to Data Availability After NDS Filing)

a) Study Characteristics

TMC114IFD3013 (EMERALD) is an ongoing, active-controlled, open-label, phase III RCT in ART-experienced patients with HIV-1 infection and virologic suppression who either switched to D/C/F/TAF FDC or continued their regimen of a boosted PI (bPI) combined with F/TDF.

Table 11: Summary of Study Characteristics for TMC114IFD3013[22, 25]

Characteristics		Details for TMC114IFD3013 (EMERALD)
Study Design	**Objective**	Pivotal efficacy and safety study
	Blinding	Open-label (not blinded due to the uneven pill burden in the two treatment groups)
	Study period	April 2015 to February 2017
	Study centres	106 study centres: Belgium (6), Canada (7), France (11), Poland (5), Spain (17), Sweden (4), Switzerland (3), UK (7), US (46)
	Design	Noninferiority
Study Population	**Randomized (N)**	1,141
	Inclusion criteria	• Currently being treated with a stable ART consisting of a bPI (limited to DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv) combined with F/TDF only, for at least 6 consecutive months preceding screening • Documented evidence of virologic suppression while on a stable ART prior to screening • Absence of history of failure on DRV treatment and absence of DRV resistance-associated mutations (including V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V), if documented historical genotypes were available • Screening eGFR ≥ 50 mL/min
	Exclusion criteria	• Had a new AIDS-defining condition diagnosed within 30 days prior to screening • Had proven or were suspected to have acute hepatitis within 30 days prior to screening • Were hepatitis C antibody–positive • Were hepatitis B surface antigen–positive

Characteristics		Details for TMC114IFD3013 (EMERALD)
		• Were patients with history of cirrhosis as diagnosed based on local practices
Drugs	**Intervention**	Single D/C/F/TAF (800 mg/150 mg/200 mg/10 mg) FDC tablet once daily
	Comparator(s)	Continue current regimen consisting of a bPI (DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv) combined with F/TDF (200 mg/300 mg) FDC once daily
Duration	**Run-in**	Not applicable
	Treatment	48 weeks
	Follow-up	After week 48, patients in both the investigational and control groups received D/C/F/TAF FDC tablets during a single-group treatment phase up to week 96 (ongoing). After week 96, patients attended visits every 6 months.
Outcomes	**Primary End Point(s)**	Virologic rebound by week 48
	Other End Points	Proportion of patients with virologic rebound through week 24 in the 2 treatment groups HIV-1 RNA, week 24 and week 48 CD4+ count, week 24 and week 48 Safety and tolerability
Notes	**Publications**	Orkin C, Molina JM, Negredo E, Arribas JR, Gathe J, Eron JJ, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomized, noninferiority trial. The Lancet HIV. 2017. Epub 2017/10/11. doi: 10.1016/s2352-3018(17)30179-0. PubMed PMID: 28993180. NCT02269917

ART = antiretroviral therapy; ATV = atazanavir; bPI = boosted protease inhibitor; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; eGFR = estimated glomerular filtration rate; FDC = fixed-dose combination; F/TDF = emtricitabine/tenofovir disoproxil fumarate; LPV = lopinavir; rtv = ritonavir; TDF = tenofovir disoproxil fumarate.

Intervention and Comparators

Patients were randomized in a 2:1 ratio to one of the following two treatment arms:

- Treatment arm 1 (test): switch to regimen of a single D/C/F/TAF (800 mg/150 mg/200 mg/10 mg) FDC tablet once daily
- Treatment arm 2 (control): continue current regimen of a bPI combined with F/TDF; allowed bPIs were DRV once daily with ritonavir (rtv) or COBI, atazanavir (ATV) with rtv or COBI, and lopinavir (LPV) with rtv.

No concomitant medications were required. Any medications different from the investigational medication had to be recorded.

Outcomes

The primary efficacy end point was the proportion of patients with confirmed virologic rebound through week 48. Virologic rebound was defined as 1) confirmed HIV-1 RNA ≥ 50 copies/mL up to and including the upper bound of the week 48 window (i.e., 54 weeks), and 2) last available on-treatment (single) HIV-1 RNA ≥ 50 copies/mL at premature discontinuation (irrespective of reason). In addition, any patient with last available on-treatment HIV-1 RNA ≥ 50 copies/mL at the study cut-off of week 48 (i.e., any last viral load test or retest having occurred no later than six weeks after week 48) was considered to have a virologic rebound.

Safety was evaluated based on AEs, clinical laboratory tests (hematology, urine chemistry, serum chemistry, urinalysis, urine renal biomarkers, serum cystatin C, metabolic panel, pregnancy testing, and hepatitis testing), physical examinations, vital signs, and bone investigation substudy (bone biomarkers and dual-energy X-ray absorptiometry scans of spine and hip).

Statistical Analyses

- A formal Data Monitoring Committee analysis for monitoring purposes including a futility analysis for lack of (noninferior) efficacy and a blinded sample size re-estimation.
- The planned week-24 interim analysis: once all patients completed the week-24 assessments or discontinued earlier. This analysis was done mainly to evaluate the safety and tolerability of D/C/F/TAF. However, efficacy of the two treatment groups was also evaluated. Results were also shared with the external, independent Data Monitoring Committee.
- The primary analysis: once all patients from the D/C/F/TAF group completed the week-48 assessments or discontinued earlier, or all patients from the control group completed the week-52 assessments or discontinued earlier (whichever came last).
- A week-96 analysis: as the study was ongoing, this analysis was planned to be performed when all patients complete the week-96 assessments or discontinue earlier.
- The final analysis: once all patients completed the extension phase assessments and the 30-day follow-up visit (if applicable) or discontinued earlier.

A sample size of 1,100 patients was expected to yield 89% power, based on the assumptions of an equal rebound rate of 4% in both treatment groups, a noninferiority margin of 4%, and a significance level of 0.025 in a one-sided test. All efficacy analyses were conducted on the ITT analysis set. Key efficacy analyses were also conducted on the PP analysis set. The ITT analysis set included all patients who were randomized and received at least one dose of treatment in the study, while the PP analysis set included all patients who 1) were randomized into the study, 2) received at least one dose of treatment in the study, and 3) did not have any major protocol deviation that was considered to potentially affect efficacy outcomes. In addition, patients with a baseline HIV-1 RNA value ≥ 50 copies/mL and patients with treatment adherence < 65% were excluded from the PP analysis set.

b) Results

Baseline Characteristics

There were 66 patients (5.8%) recruited from Canada. No relevant differences in demographic and baseline characteristics were observed between the treatment groups.

Table 12: Summary of Baseline Characteristics for TMC114IFD3013 (EMERALD)[22, 25]

Characteristic	D/C/F/TAF	Control	Total
Analysis set: ITT, N	**763**	**378**	**1,141**
Age at screening (years)			
N	763	378	1,141
[redacted]	[redacted]	[redacted]	[redacted]
Median (min to max)	46.0 (19 to 75)	45.0 (20 to 78)	46.0 (19 to 78)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	D/C/F/TAF	Control	Total
[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]
Gender, n (%)			
N	763	378	1,141
Female	140 (18.3)	65 (17.2)	205 (18.0)
Male	623 (81.7)	313 (82.8)	936 (82.0)
Race, n (%)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
N	757	376	1,133
White	573 (75.7)	282 (75.0)	855 (75.5)
Black or African American	155 (20.5)	82 (21.8)	237 (20.9)
Other	29 (3.8)	12 (3.2)	41 (3.6)
HIV-1 viral load, n (%)			
N	763	378	1,141
< 50 copies/mL	747 (97.9)	371 (98.1)	1,118 (98.0)
≥ 50 copies/mL	16 (2.1)	7 (1.9)	23 (2.0)
CD4+ (cells/mm^3)			
N	763	378	1,141
[redacted]	[redacted]	[redacted]	[redacted]
Median (min to max)	630.0 (468 to 806)	624.0 (466 to 795)	628.0 (468 to 802)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
$eGFR_{CG}$			
N	761	378	1,139
[redacted]	[redacted]	[redacted]	[redacted]
Median (min to max)	104.2 (47 to 315)	103.3 (36 to 230)	104.2 (36 to 315)
[redacted]	[redacted]	[redacted]	[redacted]

COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; $eGFR_{CG}$ = estimated glomerular filtration rate calculated using the Cockcroft–Gault method.

Patient Disposition

In total, 1,141 of the 1,299 screened patients were enrolled in the study and received at least one dose of study drug. The screening failure rate was 12.2%. The most common reason was the absence of documented evidence of virologic suppression while on a stable ART prior to screening. The majority of patients were still in the study at the time of the week-48 visit (95.5% and 94.7% in the D/C/F/TAF and control group, respectively). Discontinuation rates up to week 48 were similar in both groups.

Table 13: Summary of Patient Disposition for TMC114IFD3013 (EMERALD)[22, 25]

Disposition	TMC114IFD3013	
	D/C/F/TAF	Control
Screened	1,299	
Randomized, N	766	383
Discontinued, N (%)	34 (4.5)	20 (5.3)
WDAEs	11 (1.4)	4 (1.1)
Death	0	0
Lost to follow-up	5 (0.7)	5 (1.3)
Patient non-compliance	2 (0.3)	0
Withdrew consent	10 (1.3)	8 (2.1)
Intention-to-treat (ITT), N	763	378
Per-protocol (PP), N	721	358
Safety, N	763	378

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intention-to-treat; NR = not reported; PP = per-protocol ; WDAE = withdrawal due to adverse event.

Efficacy

The protocol-defined virologic rebound rate (confirmed HIV-1 RNA ≥ 50 copies/mL or premature discontinuations with last viral load ≥ 50 copies/mL) through week 48 in the ITT analysis set was low and similar in both treatment groups (19/763 [2.5%] versus 8/378 [2.1%] in the D/C/F/TAF and control groups, respectively). D/C/F/TAF was noninferior to the control (i.e., upper limit of the stratified MH 95% CI < 4%): the treatment difference between D/C/F/TAF and control was 0.4% (95% CI, –1.5 to 2.2); with a corresponding one-sided noninferiority $P < 0.0001$. Results were consistent in the PP population and across various subgroups, such as subgroups by bPI, adherence, and demographic characteristics.

No resistance associated with any of the study drugs was observed post baseline. The D/C/F/TAF group had a higher adherence rate (median 99.70%, range 80.0% to 134.8%) than the control group (median 98.3%, range 0% to 200%).

Table 14: TMC114IFD2HTX3013 (EMERALD) — Virologic Rebound and Response Rates Through Week 48, According to FDA Snapshot Approach

	D/C/F/TAF	Control	D/C/F/TAF Versus Control	
			P Value [a]	Difference in Percentage (95% CI)
ITT analysis set	N = 763	N = 378		
HIV-1 RNA ≥ 50 copies/mL through week 48, n (%), 95% CI	19 (2.5%), 1.5% to 3.9%	8 (2.1%), 0.9% to 4.1%	< 0.0001	0.4% (–1.5% to 2.2%)
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; C = cobicistat; D = darunavir; F = emtricitabine; ITT = intention-to-treat; NR = not reported; PP = per-protocol; RNA = ribonucleic acid; TAF = tenofovir alafenamide.

[a] One-sided *P* value for noninferiority of D/C/F/TAF versus control (margin = 4%) from the Mantel–Haenszel test adjusting for bPI at screening (ATV with rtv or COBI, DRV with rtv or COBI, and LPV with rtv).

Source: Clinical Study Report for EMERALD.[4]

2.2 Critical Appraisal of Pivotal Clinical Studies

2.2.1 Internal Validity

Randomization in the three RCTs (GS-US-299-0102,[2] AMBER,[3] and EMERALD[4]) was conducted using appropriate methods, such as the interactive voice/Web response system or a computer-generated schedule, to ensure balance across treatment groups in each stratum of the stratification factors. Patients were stratified according to important baseline factors, such as HIV-1 RNA level, CD4+ cell count, or bPI used at screening. Two trials (GS-US-299-0102[2] and AMBER[3]) were blinded, and one (EMERALD[4] was open-label. Usually in clinical trials, lack of blinding could bias the study results. However, because the key outcomes (virologic response measured with viral load) in EMERALD were objective, lack of blinding is less likely to affect the interpretation of the results. Demographic and disease characteristics at baseline were similar between treatment groups.

The rates of discontinuation were similar between treatment groups in the three studies. In the phase II GS-US-299-0102 study, 18% of patients in the D/C/F/TAF group discontinued the treatment compared with 16% in the control group. The rates of study drug discontinuation were lower in the two phase III studies, ranging from 5% to 8%. Important covariates, such as baseline HIV RNA levels, baseline CD4+ cell count, or prior bPI use, were adjusted for in the primary efficacy analysis in AMBER and EMERALD. Although the use of a PP analysis is typically considered a more conservative approach for the primary analysis in a noninferiority trial, the primary analysis in all three studies was conducted using an FAS or ITT analysis set, with a PP analysis used to investigate the robustness of the results. In the three trials, patients in the FAS or ITT analysis set were required to receive at least one dose of the study drug (which is different from a true ITT set or FAS); however, almost all randomized patients (99% to 100%) were included in the FAS or ITT analysis. In general, the results were similar between the FAS/ITT and PP analysis. However, in the phase II trial,[2] the virologic response rate at week 48 was 76.7% in the D/C/F/TAF group but 84.0% in the DRV + COBI + F/TDF group (difference –6.2%, 95% CI –19.9 to 7.4) using the FAS analysis set; it was 92.9% for D/C/F/TAF and 91.3% for the control group (difference 2.4%; 95% CI, –8.8 to 13.7) using the PP analysis set (Table 6). The manufacturer indicated that the discrepancy may be partially explained by the different proportion of patients who discontinued treatment for reasons other than “lack of efficacy,” such as investigator’s discretion, withdrawal of consent, withdrawal due to AEs, patient non-compliance, protocol violation, pregnancy, or study discontinuation by sponsor. In total, nine patients (8.7%) in the D/C/F/TAF group and two patients (4.0%) in the control group discontinued the treatment in this study. Results of patient disposition showed that the reasons for discontinuation were somewhat different between the two treatment groups (Table 5), but the differences did not adequately justify the lower response rate in the D/C/F/TAF group at week 48. At week 48, 83% and 92% of patients from the original randomized set were included in the PP analysis for the D/C/F/TAF group and the control group, respectively, while all randomized patients were included in the FAS data sets in this study.

Overall, the rates of virologic success for D/C/F/TAF across the studies were lower than those observed for other combination therapy in usual clinical practice (approximately 88% to 99%).[6,7] This may be due to the greater flexibility (in choosing regimens) that clinicians have in treating patients with HIV infection in everyday settings.

In GS-US-299-0102,[2] alpha was not adjusted because the study was exploratory in nature. In AMBER and EMERALD,[3,4] adjustment of inflated type 1 error was not performed in the primary or secondary analysis.

In GS-US-299-0102, missing HIV-1 RNA values were treated as virologic failure (HIV-1 RNA ≥ 50 copies/mL) or excluded from the computation of virologic response. The rate of virologic suppression was higher when missing data were excluded (83.7% at week 24 for D/C/F/TAF) than when such data were treated as failure (74.8% at week 24 for D/C/F/TAF). In AMBER, missing HIV-1 RNA data were imputed with the patient's baseline value, or using the last observation carried forward approach. There were no results specifically reported after missing data imputation. The EMERALD study did not specify how missing data were handled. The FDA guidance document indicates that analyses excluding patients with missing data are potentially biased, because patients who do not complete the trial may differ substantially in both measured and unmeasured ways from patients who remain in the trial.[8]

Subgroup analyses were conducted on virologic outcomes in the three studies, based on patients' baseline demographic characteristics, disease characteristics, as well as treatment adherence. However, it is unclear whether these subgroups were pre-defined in the protocol phase. In addition, the validity of the subgroup analysis is questionable owing to the lack of power to detect statistically significant differences between treatment groups and the lack of a test of significance of interaction.

2.2.2 External Validity

The proportion of patients who failed the screening was 34% in the GS-US-299-0102 study,[2] 16.3% in AMBER,[3] and 11.5% in EMERALD.[4] The reasons for screening failure were not provided. This is a limitation of the studies. Canadian patients were enrolled in AMBER (32, 4.4%) and EMERALD (66, 5.8%). Patients with hepatitis B or hepatitis C coinfection were excluded from all three studies, which leaves uncertain the relative efficacy and safety in these subgroups. These patients' baseline demographic characteristics and disease characteristics suggested that they had relatively mild disease and normal renal function. The clinical expert consulted for this review indicated that such characteristics were similar to those of the average untreated or newly diagnosed patients with HIV infection in Canada, but less likely to reflect an average patient overall, as the vast majority of identified patients are on treatment and have a suppressed viral load.

Patients enrolled in EMERALD were required to have been on a stable ART consisting of a bPI (such as DRV once daily with rtv or COBI, atazanavir with rtv or COBI, or lopinavir with rtv) combined with F/TDF only, for at least six consecutive months prior to screening. According to the clinical expert, these were commonly used ART drugs, and the patients usually have a high level of adherence to HIV treatment in clinical practice.

The manufacturer requested that D/C/F/TAF be reimbursed as a complete regimen for the treatment of HIV-1 infection in both adults and adolescents. All of the three included clinical trials recruited adult patients only; therefore, there is a lack of direct evidence to support the use of D/C/F/TAF in adolescents. According to the product monograph of this drug, although the safety of D/C/F/TAF in pediatric patients has not been investigated, the safety of its components (DRV with ritonavir, and an FDC containing elvitegravir [E], COBI, FTC, and

TAF) has been evaluated in patients aged 12 to < 18 years and weighting at least 40 kg through previous clinical trials. Findings of these studies suggested that the overall safety profile in this particular group was similar to that observed in the adult population. The clinical expert consulted for this review confirmed that the results relevant to the components of D/C/F/TAF can be generalized to D/C/F/TAF FDC; however, bone abnormalities may be a concern in adolescents and need to be monitored closely.

The primary end point assessed in these studies was in accordance with the FDA recommendations on the development program and clinical trial designs for ARTs for the treatment of HIV infection (i.e., use of the snapshot approach to assess virologic outcomes at week 48).[8] The snapshot method was adopted in all three trials. Virologic response was evaluated at week 48 in the two phase III studies (virologic response in AMBER[3] and virologic rebound in EMERALD[4]) and at week 24 in the phase II study GS-US-299-0102[2]. The use of a noninferiority margin (10% to 12% for the end point of HIV RNA < 50 copies/mL at 48 weeks; 4% for virologic rebound in switch trials — patients whose HIV-1 is fully suppressed on an initial regimen are randomized to either continue their current regimen or to change one of the drugs in their existing regimen to a new drug) is consistent with the FDA guidance.

Clinically important outcomes, such as health-related quality of life, were not assessed in the three studies. Furthermore, there are seven STRs currently available in Canada (Atripla, Complera, Odefsey, Stribild, Genvoya, Triumeq, and Symtuza). It would be valuable to evaluate the clinical benefits and harms of Symtuza relative to the other STRs for the treatment of HIV-1 infection.

2.3 Summary of Safety

The safety profile of D/C/F/TAF is primarily based on the safety profiles of DRV/COBI and F/TAF combined with data from the phase II double-blind study GS-US-299-0102 (N = 153; 103 patients on D/C/F/TAF). The D/C/F/TAF phase I studies (Section 2.4) involving 270 healthy participants (of which 231 received the D/C/F/TAF FDC; studies TMC114FD2HTX1001, TMC114FD2HTX1002, and GS-US-299-0101) provide further supportive safety data for the D/C/F/TAF FDC. These phase I and II studies are included in the NDS for Health Canada review.

The main focus of this section is a summary of safety data from GS-US-299-0102, as this is the key clinical study in the NDS for the target population. Safety data from the two phase III studies with D/C/F/TAF FDC in 725 ART-naive (AMBER) and in 1,149 patients with HIV-1 infection and viral suppression (EMERALD) are also summarized; however, two phase III studies were not submitted to Health Canada, since data became available only after the NDS submission.

2.3.1 Safety Evaluation Plan

No pooling or comparison of the studies is considered appropriate due to differences in design. In the NDS, GS-US-299-0102 is the only phase II clinical study in the target population involving the to-be-marketed D/C/F/TAF formulation.

The AEs reported during GS-US-299-0102 were reviewed by medical experts for identification of adverse drug reactions (ADRs) associated with D/C/F/TAF. To evaluate the safety and tolerability of the treatment regimens, these safety assessments were performed:

AEs and clinical laboratory tests, including BMD using dual-energy X-ray absorptiometry, bone biomarkers (C-type collagen sequence and procollagen type 1 N-terminal propeptide), serum creatinine, estimated glomerular filtration rate by three formulas (Cockcroft–Gault and Chronic Kidney Disease Epidemiology Collaboration creatinine and cystatin C), and renal biomarkers (urine retinol-binding protein [RBP], beta-2-microglobulin, RBP-to-creatinine ratio, beta-2-microglobulin–to-creatinine ratio, urine protein-to-creatinine ratio, and urine albumin–to-creatinine ratio).

2.3.2 Safety Populations Evaluated

GS-US-299-0102 was a phase II, double-blind, multi-centre, active-controlled RCT to evaluate the safety and efficacy of D/C/F/TAF FDC versus COBI-boosted DRV (DRV + COBI) + F/TDF FDC in 153 treatment-naive adult patients with HIV-1 infection (103 in the D/C/F/TAF FDC group; 50 in the DRV + COBI + F/TDF group). The median duration of study drug exposure was 68.0 weeks. Safety analyses were performed on the safety analysis set.

2.3.3 Overview of Safety

Table 15: Summary of Treatment-Emergent Adverse Events — GS-US-299-0102[21,23]

n (%) of Patients Experiencing	D/C/F/TAF FDC (N = 103)	DRV + COBI + F/TDF (N = 50)
Treatment-emergent AE	95 (92.2)	47 (94.0)
Any Grade 2, 3, or 4 AE	57 (55.3)	24 (48.0)
Any Grade 3 or 4 AE	7 (6.8)	4 (8.0)
Any study drug–related AE	43 (41.7)	19 (38.0)
Any Grade 2, 3, or 4 study drug–related AE	10 (9.7)	3 (6.0)
Any Grade 3 or 4 study drug–related AE	1 (1.0)	1 (2.0)
Any SAE	5 (4.9)	2 (4.0)
Any study drug–related SAE	1 (1.0)	0
Any AE leading to premature study drug discontinuation	2 (1.9)	2 (4.0)
Death	0	0

AE = adverse event; COBI or C = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV or D = darunavir; FDC = fixed-dose combination; F/TDF = emtricitabine/tenofovir disoproxil fumarate; SAE = serious adverse event.

No patients died during the study. Similar percentages of patients in each group had any AE (D/C/F/TAF 92.2%, 95 patients; DRV + COBI + F/TDF 94.0%, 47 patients) or any AE considered by the investigator to be related to study drug (D/C/F/TAF 41.7%, 43 patients; DRV + COBI + F/TDF 38.0%, 19 patients). Any Grade 3 or 4 AE was reported for 6.8% of patients (n = 7) in the D/C/F/TAF group, and 8.0% of patients (n = 4) in the DRV + COBI + F/TDF group. Any serious adverse event (SAE) was reported for 4.9% of patients (n = 5) in the D/C/F/TAF group and 4.0% of patients (n = 2) in the DRV + COBI + F/TDF group.

Any Grade 2, 3, or 4 AE was reported for 55.3% of patients (n = 57) in the D/C/F/TAF group and 48.0% of patients (n = 24) in the DRV + COBI + F/TDF group. Any Grade 2, 3, or 4 AE considered by the investigator to be related to study drug was reported for 9.7% of patients (n = 10) in the D/C/F/TAF group and 6.0% of patients (n = 3) in the DRV + COBI + F/TDF group.

One patient in each treatment group had a Grade 3 or 4 AE considered by the investigator to be related to study drug. Two patients (1.9%) in the D/C/F/TAF group and two patients (4.0%) in the DRV + COBI + F/TDF group had any AE leading to premature study drug discontinuation. In the D/C/F/TAF group, one patient discontinued study drug due to an SAE of substance abuse, and the other discontinued study drug due to an SAE (hypersensitivity) and a nonserious AE (rash), both related to the study drug. In the DRV + COBI + F/TDF group, one patient discontinued the study drug due to an SAE of renal tubular disorder (reported as proximal renal tubulopathy), and another patient discontinued the study drug due to a study drug–related nonserious AE of worsening of diarrhea. Two patients in the D/C/F/TAF group had AIDS-defining events (Centers for Disease Control Class C): one nonserious Kaposi's sarcoma and one nonserious HIV wasting syndrome. One patient in the DRV + COBI + TVD group had an AIDS-defining event of nonserious Kaposi's sarcoma.

AEs that occurred in ≥ 5% patients were consistent with those expected in the target population and with the known safety profiles of the study drugs. The AEs reported for ≥ 10% of patients in either treatment group were as follows: 1) D/C/F/TAF group — diarrhea (21.4%, 22 patients); upper respiratory tract infection (15.5%, 16 patients); fatigue (13.6%, 14 patients); nausea (12.6%, 13 patients); and rash (11.7%, 12 patients); 2) DRV + COBI + F/TDF group — diarrhea (26.0%, 13 patients); fatigue (18.0%, nine patients); upper respiratory tract infection (14.0%, seven patients); flatulence (12.0%, six patients); and nausea, pain in extremity, vitamin D deficiency, and vomiting (each in 10.0%, five patients).

Renal Safety

Patients who received D/C/F/TAF showed a better renal safety profile than those who received DRV + COBI + F/TDF, as evidenced by significantly less reduction in eGFR and less tubular proteinuria. There were no cases of proximal renal tubulopathy (including Fanconi syndrome) reported in patients infected with HIV-1 receiving D/C/F/TAF; one case was reported in the DRV + COBI + F/TDF group. Increases from baseline in mean values for serum creatinine were smaller in the D/C/F/TAF group than in the DRV + COBI + F/TDF group. Increases in serum creatinine and concomitant changes in estimated glomerular filtration rate (Cockcroft–Gault) occurred by week 2 of treatment and remained stable through 48 weeks. Changes from baseline with D/C/F/TAF were smaller than with DRV + COBI + F/TDF. There were statistically significant differences between the treatment groups, favouring D/C/F/TAF, in change from baseline in RBP-to-creatinine and beta-2-microglobulin–to-creatinine ratios.

Bone Safety

At week 48, patients receiving D/C/F/TAF experienced significantly less decline in BMD than those receiving DRV + COBI + F/TDF. A smaller proportion of patients in the D/C/F/TAF group compared with those in the DRV + COBI + F/TDF group had a clinically significant (> 3%) decrease from baseline in hip BMD (18.3% versus 61.7%) and in spine BMD (32.5% versus 55.3%). Increases from baseline in the bone turnover biomarkers type I collagen C-telopeptide (a bone resorption biomarker) and procollagen type 1 N-terminal propeptide (a bone formation biomarker), as well as parathyroid hormone (a hormone involved in bone metabolism) were smaller in the D/C/F/TAF group than in the DRV + COBI + F/TDF group at both weeks 24 and 48.

Fasting Lipid Parameters

The median increase in fasting lipid parameters from baseline was greater in the D/C/F/TAF group than in the DRV + COBI + F/TDF group at both week 24 and week 48. Statistically significant differences between the two groups in change from baseline were seen for fasting total cholesterol and fasting direct low-density lipoprotein (LDL) cholesterol at week 24 ($P = 0.014$ for the difference between treatment groups for total cholesterol, $P = 0.004$ for direct LDL cholesterol, $P = 0.35$ for high-density lipoprotein [HDL] cholesterol, and $P = 0.13$ for triglycerides), and for all four lipid parameters at week 48 ($P < 0.001$ for the difference between treatment groups for total cholesterol and direct LDL cholesterol, $P = 0.009$ for HDL cholesterol, and $P = 0.007$ for triglycerides). There were no clinically relevant changes from baseline for either treatment group or statistically significant differences in changes from baseline between treatment groups for median fasting total cholesterol–to-HDL ratio. Changes in lipid parameters in the D/C/F/TAF phase II study were consistent with those in the E/C/F/TAF studies in ART-naive patients and with the changes observed with DRV/COBI and DRV/rtv.

Pediatric Patients

The safety of COBI and F/TAF were evaluated in a single-arm clinical study (GS-US-292-0106) in which treatment-naive pediatric patients aged 12 to < 18 years with HIV-1 infection received E/C/F/TAF as an FDC tablet. Results from this study show that the E/C/F/TAF FDC is well tolerated in adolescents, with a low incidence of study drug–related SAEs and no AEs leading to discontinuation of study drug. There were no notable changes from baseline in height-age–adjusted spine and total body less head BMD Z-scores after 48 weeks of treatment, indicating that patients mineralized bone at rates consistent with those of the reference population. Few patients experienced a clinically relevant decrease from baseline in BMD. These data supported the approval of E/C/F/TAF with a COBI dose of 150 mg and an F/TAF dose of 200/10 mg once daily for use in adolescents weighing at least 35 kg.[12, 26, 27]

Safety Data from Phase III Studies TMC114FD2HTX3001 (AMBER) and TMC114IFD3013 (EMERALD)[3,4]

[redacted]

In EMERALD, the risks of treatment-emergent AEs, SAEs, and withdrawal due to AEs were similar between D/C/F/TAF and the control (Table 16). The most frequently reported AEs in both treatment groups were nasopharyngitis and upper respiratory tract infection (both in 10.6% versus 10.3% of patients). No deaths occurred up to the week-48 visit in this study.

Results from the week-48 analyses of both phase III studies demonstrate that treatment with D/C/F/TAF FDC was well tolerated across all patient populations evaluated, and no new ADRs were identified beyond the known ADRs for the individual components of D/C/F/TAF.

Table 16: Summary of Adverse Events — Interim Results of AMBER[3] and EMERALD[4]

	AMBER		EMERALD	
n (%) of Patients Experiencing	D/C/F/TAF (N = 362)	DRV + COBI + F/TDF (N = 363)	D/C/F/TAF (N = 763)	bPI + F/TDF (N = 378)
Any treatment-emergent AEs	312 (86.2%)	307 (84.6%)	625 (81.9%)	311 (82.3%)
Any SAEs	17 (4.7%)	21 (5.8%)	35 (4.6%)	18 (4.8%)
WDAEs	7 (1.9%)	16 (4.4%)	11 (1.4%)	5 (1.3%)
Death	0	0	0	0

AE = adverse event; bPI = boosted protease inhibitor; C or COBI = cobicistat; D or DRV = darunavir; F = emtricitabine; SAE = serious adverse event; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; WDAE = withdrawal due to adverse event.

Sources: Clinical Study Reports for AMBER[3] and EMERALD.[4]

Summary

The safety profile of the D/C/F/TAF FDC is based on the well-established safety profile of the individual components. The safety profile of D/C/F/TAF FDC is supported by the results from the phase II double-blind study GS-US-299-0102 (in the NDS) and as well as from the two phase III studies AMBER and EMERALD (not contained in the NDS). The observed safety profile is in line with expectations and did not raise additional concerns.

2.4 Bioequivalence

The bioequivalence of Symtuza (D/C/F/TAF FDC) to its individual components is supported by the pivotal bioequivalence study TMC114FD2HTX1001 and the relative bioavailability studies TMC114FD2HTX1002 and GS-US-299-0101. The studies provide a PK bridge between the D/C/F/TAF FDC and the two approved combinations DRV/COBI (800 mg/150 mg) and F/TAF (200 mg/10 mg).

GS-US-299-0101 is a relative bioavailability study that evaluated different prototype FDC formulations (monolayer and bilayer). It compared three candidate D/C/F/TAF FDC tablet formulations after repeated administration in order to select a formulation for phase II.[29] The D/C/F/TAF 800 mg/150 mg/200 mg/10 mg FDC monolayer tablet was chosen for further development. In a subsequent part of the study, the bioavailability of DRV, COBI, FTC, TAF, and TFV was evaluated when administered as the D/C/F/TAF 800 mg/150 mg/200 mg/10 mg FDC and compared with the combination of DRV 800 mg + COBI 150 mg in one panel and compared with FTC 200 mg + TAF 25 mg in another panel. Based on C_{max} and AUC, following administration of D/C/F/TAF FDC (TAF 10 mg), single-dose TAF exposures were lower than and TFV exposures were similar to those after administration of FTC + TAF (25 mg).[29] The monolayer formulation containing 10 mg TAF was selected as the phase II formulation and was subsequently used in study GS-US-299-0102 in patients with HIV-1 infection. This intended commercial formulation (G001) of the D/C/F/TAF FDC was used in the pivotal bioequivalence study TMC114FD2HTX1001 as well as in the food effect study TMC114FD2HTX1002.

Pivotal Bioequivalence Study TMC114FD2HTX1001

A summary of the PK parameters for this study is presented in Table 17. The D/C/F/TAF 800 mg/150 mg/200 mg/10 mg FDC tablet is bioequivalent to combined administration of the separate drugs DRV, the F/TAF FDC, and COBI, with respect to both rate and extent of absorption of the four components involved. The 90% CIs of the least squares mean ratios

of all main PK parameters for all four compounds (DRV, COBI, FTC, TAF) were within the acceptance range of 80.00% to 125.00%.[30]

Food Effect Study TMC114FD2HTX1002

A summary of the PK parameters for this study is presented in Table 17. The exposure to DRV, COBI, FTC, and TAF was shown to be similar when administered either as D/C/F/TAF FDC or separately DRV + COBI + F/TAF. The impact of food on the PK of COBI, FTC, and TAF is not considered to be clinically relevant; however, based on the improved absorption of DRV in fed condition and in line with other DRV-containing formulations, it is recommended that the D/C/F/TAF FDC tablet be taken with food.[31]

DRV, COBI, and FTC possess uncomplicated PK characteristics. DRV exhibits linear PK, with first-order absorption and elimination.[32] COBI in plasma shows time- and dose-dependent PK. FTC in plasma shows linear, first-order PK. Following once daily administration of FDC, the TAF exposure parameters AUC_{tau} and C_{max} were lower (approximately 30% and 25%), compared with exposures following a single dose, consistent with a mixed inhibitory/inductive effect on TAF absorption, indicative of nonlinear PK of TAF in time.[11, 12, 26, 33, 34 35]

Table 17: Bioequivalence Profile for Combination Product

Study TMC114FD2HTX1001	DRV as D/C/F/TAF FDC[a]	DRV as DRV + F/TAF FDC + COBI[b]	FTC as D/C/F/TAF FDC[a]	FTC as DRV + F/TAF FDC + COBI[b]	TAF as D/C/F/TAF FDC[a]	TAF as DRV + F/TAF FDC + COBI[b]	COBI as D/C/F/TAF FDC[a]	COBI as DRV + F/TAF FDC + COBI[b]
AUC_{last}	N = 93	N = 95	N = 93	N = 95	N = 94	N = 96	N = 93	N = 95
Mean	87,200	84,406	11,722	11,746	123	132	6,681	6,763
Standard deviation	27,385	29,481	1,959	1,868	42.0	58.1	2,486	2,436
Ratio of LS means (90% CI)	104.84 (100.87 to 108.97)		100.04 (98.46 to 101.66)		96.59 (91.72 to 101.73)		98.77 (95.14 to 102.52)	
C_{max}	N = 93	N = 95	N = 93	N = 95	N = 94	N = 96	N = 93	N = 95
Mean	7,042	6,620	2041	2,053	110	120	894	881
Standard deviation	1,481	1,429	481	469	54.1	74.0	254	207
Ratio of LS means (90% CI)	106.73 (103.50 to 110.06)		99.32 (95.61 to 103.17)		96.87 (88.95 to 105.50)		100.69 (96.80 to 104.73)	
T_{max}	N = 93	N = 95	N = 93	N = 95	N = 94	N = 96	N = 93	N = 95
Median	4.00	4.00	2.00	2.00	1.50	1.01	4.00	4.00
Range	1.50 to 8.00	2.00 to 12.00	0.60 to 5.00	0.50 to 8.00	0.25 to 3.50	0.25 to 4.00	1.50 to 5.05	1.50 to 5.05
Study TMC114FD2HTX1002	**FTC as D/C/F/TAF FDC[a]**	**FTC as E/C/F/TAF FDC[c]**	**FTC as D/C/F/TAF FDC[a]**	**FTC as DRV + F/TAF FDC + COBI[b]**	**FTC as D/C/F/TAF FDC[a], fasted**	**FTC as D/C/F/TAF FDC[a], fed**	**TAF as D/C/F/TAF FDC[a]**	**TAF as E/C/F/TAF FDC[c]**
AUC_{last}	N = 24	N = 24	N = 24	N = 24	N = 24	N = 24	N = 24	N = 24
Mean	10,595	10,851	10,365	10,341	11,593	11,499	114	165
Standard deviation	1,777	1964	1,753	1,455	2,573	2,055	55.8	85.1
Ratio of LS means (90% CI)	97.86 (95.82 to 99.94)		99.91 (97.36 to 102.52)		100.12 (96.29 to 104.10)		69.87 (62.82 to 77.72)	
C_{max}	N = 24	N = 24	N = 24	N = 24	N = 24	N = 24	N = 24	N = 24
Mean	1,691	1,789	1,677	1,828	2,247	1,785	102	124
Standard deviation	414	353	411	478	573	486	62.0	67.3
Ratio of LS means (90% CI)	94.05 (87.78 to 100.77)		92.16 (84.40 to 100.63)		125.99 (112.85 to 140.65)		79.92 (64.30 to 99.34)	
T_{max}	N = 24	N = 24	N = 24	N = 24	N = 24	N = 24	N = 24	N = 24

Median	2.50	3.00	3.00	2.00	1.00	2.00	1.50	1.75
Range	1.00 to 5.00	1.00 to 4.00	1.00 to 4.98	1.00 to 5.00	0.50 to 2.00	0.75 to 5.00	0.50 to 5.00	0.50 to 4.00
Study TMC114FD2HTX1002	**TAF as D/C/F/TAF FDC[a]**	**TAF as DRV + F/TAF FDC + COBI[b]**	**TAF as D/C/F/TAF FDC[a], fasted**	**TAF as D/C/F/TAF FDC[a], fed**	**DRV as D/C/F/TAF FDC[a]**	**DRV as DRV + F/TAF FDC + COBI[b]**	**DRV as D/C/F/TAF FDC[a], fasted**	**DRV as D/C/F/TAF FDC[a], fed**
AUC_{last}	N = 24	N = 24	N = 24	N = 24	N = 23	N = 24	N = 23	N = 24
Mean	123	128	106	117	90,809	90,414	67,504	93,541
Standard deviation	67.8	109	44.7	51.5	44,208	57,071	35,642	39,730
Ratio of LS means (90% CI)	106.81 (93.04 to 122.61)		89.54 (81.20 to 98.72)		102.99 (97.46 to 108.83)		65.65 (56.76 to 75.92)	
C_{max}	N = 24	N = 24	N = 24	N = 24	N = 23	N = 24	N = 23	N = 24
Mean	105	120	180	107	6,670	6,554	4,089	6,629
Standard deviation	94.9	113	90.6	65.2	1,521	2,568	1,846	1,543
Ratio of LS means (90% CI)	91.44 (71.57 to 116.84)		182.29 (140.50 to 236.50)		104.32 (96.95 to 112.26)		54.99 (46.73 to 64.71)	
T_{max}	N = 24	N = 24	N = 24	N = 24	N = 23	N = 24	N = 23	N = 24
Median	1.28	1.25	0.50	0.88	5.00	4.00	3.00	5.00
Range	0.50 to 3.00	0.25 to 3.00	0.25 to 0.75	0.25 to 5.00	2.00 to 8.00	1.50 to 8.00	1.00 to 8.02	1.50 to 8.00
Study TMC114FD2HTX1002	**COBI as D/C/F/TAF FDC[a]**	**COBI as DRV + F/TAF FDC + COBI[b]**	**COBI as D/C/F/TAF FDC[a], fasted**	**COBI as D/C/F/TAF FDC[a], fed**				
AUC_{last}	N = 24	N = 24	N = 23	N = 24				
Mean	6,224	6,668	5,771	6,168				
Standard deviation	1,886	2,349	3,206	2,260				
Ratio of LS means (90% CI)	93.96 (89.62 to 98.50)		70.90 (51.13 to 98.30)					
C_{max}	N = 24	N = 24	N = 23	N = 24				
Mean	801	874	704	711				
Standard deviation	159	197	368	164				
Ratio of LS means (90% CI)	92.12 (87.72 to 96.74)		76.96 (55.70 to 106.33)					
T_{max}	N = 24	N = 24	N = 23	N = 24				
Median	4.00	3.00	3.00	5.00				
Range	1.50 to 6.00	1.50 to 5.02	1.00 to 6.00	2.00 to 6.10				

AUC_{last} = area under the curve from 0 hours up to the time of the last measurable (non-below quantification limit) concentration after administration; AUC_{tau} = area under the curve from time of administration up to the end of the dosage interval; C or COBI = cobicistat; CI = confidence interval; C_{max} = maximum observed concentration; D or DRV = darunavir; F = emtricitabine; FDC = fixed-drug combination; LS = least squares; T_{max} = time since study drug administration until the maximum observed analyte concentration; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[a] D/C/F/TAF FDC 800 mg/150 mg/200 mg/10 mg.

[b] DRV 800 mg + FTC/TAF 200/10 mg + COBI 150 mg.

[c] E/C/F/TAF FDC 150 mg/150 mg/200 mg/10 mg.

3. Pharmacoeconomic Evaluation

3.1 Manufacturer-Submitted Cost Information

Table 18: Cost Comparison of New Combination Product and Individual Components

Drug / Comparator (Trade Name)	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)
Darunavir/cobicistat/emtricitabine/ tenofovir alafenamide	800 mg/150 mg/ 200 mg/10 mg	Tablet	$23.8672/ 28.5700	One tablet orally once daily with food	$52.4372
Darunavir (Prezista)	800 mg	Tablet	$21.7160	One tablet orally once daily with food	$21.7160
Cobicistat (Tybost)	Not available as a single drug				
Emtricitabine (Emtriva)	Not available as a single drug				
Tenofovir alafenamide	Not available as a single drug				
Total					**Not applicable**
Darunavir/ cobicistat (Prezcobix)	800 mg/150 mg	Tablet	$23.8672	One tablet orally once daily with food	$23.8672
Emtricitabine/ tenofovir alafenamide (Descovy)	200 mg/10 mg	Tablet	$28.5700	One tablet orally once daily with or without food	$28.5700
Total					**$52.4372**

Sources: Ontario Drug Database December 2017, McKesson Drug Database August 2017 (for Descovy; public listing is not available), Prezcobix Product Monograph, Prezista Product Monograph, and Descovy Product Monograph.

3.2 Manufacturer-Submitted Information Regarding Current Patent Status

Please refer to the Table 19 for current patent status.

Table 19: Summary of Patent Status

Medicinal Ingredient(s)	Patent Number	Date Granted (yyyy-mm-dd)	Expiration Date (yyyy-mm-dd)
Darunavir	2336160	2015-02-17	2019-06-23
Darunavir Darunavir/cobicistat	2485834	2007-07-17	2023-05-16
Darunavir Darunavir/cobicistat	2872424	2017-03-07	2019-06-23
Cobicistat Darunavir/cobicistat	2678907	2014-06-17	2028-02-22
Cobicistat Darunavir/cobicistat	2720856	2016-02-02	2029-05-01
Tenofovir alafenamide Emtricitabine/tenofovir alafenamide	22416757	2011-02-15	2021-07-20

dd = day; mm = month; yyyy = year.

3.3 Critical Appraisal of Cost Information

The manufacturer presented a cost comparison in which the submitted price for D/C/F/TAF FDC, $52.44 per day, is at parity with the combined publicly available prices of the available component medications DRV/COBI ($23.87 per day) and F/TAF ($28.57 per day). Although the price for F/TAF is consistent across CADTH Common Drug Review (CDR)-participating drug plans, the price of DRV/COBI varies from $23.58 to $25.90 (Table 20), indicating that the use of D/C/F/TAF FDC may lead to either cost savings or increases, depending on the jurisdiction. Of note, use of D/C/F/TAF FDC may lead to savings on the price of a dispensing fee per claim, and the price of the individual components does not consider any confidential prices. CDR also notes that most patients favour STRs over MTRs, owing to their convenient administration, according to feedback from the clinical expert.

Table 20: Darunavir/Cobicistat Price Variation Across CDR-Participating Drug Plans

Darunavir/Cobicistat Prices in CDR-Participating Drug Plans ($)							
British Columbia	**Alberta**	**Saskatchewan**	**Manitoba**	**Ontario**	**New Brunswick**	**Nova Scotia**	**Prince Edward Island**
$23.8670[a]	$23.8670[a]	$23.8670	$23.5787[a]	$23.8672	$23.8670	$23.8670[a]	$23.8670[a]
Newfoundland and Labrador	**Yukon**	**Northwest Territories**	**Nunavut**	**NIHB**	**DND**	**VAC**	
$25.8957	$23.8670[a]	$23.8670[a]	$23.8670[a]	N/A	N/A	N/A	

CDR = CADTH Common Drug Review; DND = Department of National Defence; NIHB = Non-Insured Health Benefits Program; N/A = Price not available; VAC = Veterans Affairs Canada.

Note: All prices listed are formulary prices obtained from IQVIA DeltaPA unless otherwise noted.[9] Actual price paid by the plan may vary.

[a] Wholesale acquisition price from IQVIA DeltaPA.[9]

The clinical expert consulted by CADTH for this review referred to other STRs available in Canada that could be considered comparators to D/C/F/TAF FDC. As a result, CDR compared the cost of D/C/F/TAF FDC to other quadruple- and triple-therapy STRs available on the market with similar indications.

Quadruple-therapy STRs include E/C/F/TAF (Genvoya), recommended by the US Department of Health and Human Services as the initial regimen of choice for most patients,[10] and E/C/F/TDF (Stribild). These medications are available at a daily drug cost of $46.40 and $48.02, respectively, Table 21. The price of D/C/F/TAF FDC is approximately 13.0% higher than E/C/F/TAF and 9.2% higher than E/C/F/TDF; this would result in an additional cost of $2,208 and $1,614 per year per patient, respectively. However, it is important to note that the listed price of E/C/F/TDF ranges across CDR-drug plans, from $45.52 to $52.10, Table 22.

Table 21: Cost Information Comparing Manufacturer-Submitted Price with Other Available Quadruple-Therapy STRs

Drug / Comparator (Trade Name)	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)	Yearly Drug Cost ($)
Darunavir/cobicistat/ emtricitabine/tenofovir alafenamide	800 mg/150 mg/ 200 mg/10 mg	Tablet	$52.4372	One tablet orally once daily with food	$52.4372	$19,140
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (Genvoya)	150 mg/150 mg/ 200 mg/10 mg	Tablet	$46.3894	One tablet orally once daily with food	$46.3894	$16,932
Elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate (Stribild)	150 mg/150 mg/ 200 mg/300 mg	Tablet	$48.0177	One tablet orally once daily with food	$48.0177	$17,526

Note: Prices for elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide and elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate were obtained from Ontario Drug Benefit formulary (March 19, 2018) and do not reflect any confidential negotiated prices. Yearly drug costs based on 365 days per year.

Table 22: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Price Variation Across CDR-Participating Drug Plans

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Prices in CDR-Participating Drug Plans ($)							
British Columbia	**Alberta**	**Saskatchewan**	**Manitoba**	**Ontario**	**New Brunswick**	**Nova Scotia**	**Prince Edward Island**
47.2150[a]	46.3893[a]	45.5200	48.0177[a]	48.0177	47.2150	48.0177[a]	48.0177[a]
Newfoundland and Labrador	**Yukon**	**Northwest Territories**	**Nunavut**	**NIHB**	**DND**	**VAC**	
52.0992	45.5200[a]	45.5200[a]	45.5200[a]	N/A	N/A	N/A	

CDR = CADTH Common Drug Review; DND = Department of National Defence; NIHB = Non-Insured Health Benefits Program; N/A = Price not available; VAC = Veterans Affairs Canada.

Note: All prices listed are formulary prices obtained from IQVIA DeltaPA unless otherwise noted.[9] Actual price paid by the plan may vary.

[a] Wholesale acquisition price from IQVIA DeltaPA.[9]

Triple-therapy STRs include dolutegravir/abacavir/lamivudine (Triumeq), efavirenz/lamivudine/TDF (generics), rilpivirine/FTC/TAF (Odefsey), and rilpivirine/FTC/TDF (Complera). The submitted daily price for D/C/F/TAF FDC is higher than all four triple-therapy STRs available, which would present an additional cost ranging from $2,765 (compared with rilpivirine/FTC/TDF) to $10,869 (compared with efavirenz/lamivudine/TDF) per person per year, Table 23. Of note, the listed prices for dolutegravir/abacavir/lamivudine and rilpivirine/FTC/TDF vary from $42.66 to $46.87 (Table 24) and $41.57 to $48.68 (Table 25) per tablet, respectively. Therefore, the additional cost of D/C/F/TAF FDC compared with these two STRs varies by jurisdiction.

Table 23: Cost Information Comparing Manufacturer-Submitted Price with Other Available Triple-Therapy STRs

Drug / Comparator (Trade Name)	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)	Yearly Drug Cost ($)
Darunavir/cobicistat/emtricitabine/ tenofovir alafenamide	800 mg/150 mg/ 200 mg/10 mg	Tablet	$52.4372	One tablet orally once daily with food	$52.4372	$19,140
Dolutegravir/abacavir/lamivudine (Triumeq)	50 mg/ 600 mg/300 mg	Tablet	$43.2020	One tablet orally once daily with or without food	$43.2020	$15,769
Efavirenz/emtricitabine/tenofovir disoproxil fumarate (generics)	600 mg/300 mg/ 200 mg	Tablet	$22.6600	One tablet orally once daily on an empty stomach	$22.6600	$8,271
Emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey)	200 mg/25 mg/ 25 mg	Tablet	$42.3670[a]	One tablet orally once daily with food	$42.3670	$15,464
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera)	200 mg/ 25 mg/300 mg	Tablet	$44.8643	One tablet orally once daily with food	$44.8643	$16,375

Note: Prices for efavirenz/emtricitabine/tenofovir disoproxil fumarate, emtricitabine/rilpivirine/tenofovir disoproxil fumarate, and dolutegravir/abacavir/lamivudine were obtained from Ontario Drug Benefit formulary (March 19, 2018) and do not reflect any confidential negotiated prices. Yearly drug costs based on 365 days per year.

All prices listed are formulary prices obtained from IQVIA DeltaPA unless otherwise noted.[9] Actual price paid by the plan may vary.

[a] Wholesale acquisition price from IQVIA DeltaPA.[9]

Table 24: Dolutegravir/Abacavir/Lamivudine Price Variation Across CDR-Participating Drug Plans

Dolutegravir/Abacavir/Lamivudine Prices in CDR-Participating Drug Plans ($)							
British Columbia	**Alberta**	**Saskatchewan**	**Manitoba**	**Ontario**	**New Brunswick**	**Nova Scotia**	**Prince Edward Island**
$43.2020[a]	$43.2020[a]	$43.2020	$42.0663[a]	$43.2020	$43.2020	$43.2020[a]	$43.2020[a]
Newfoundland and Labrador	**Yukon**	**Northwest Territories**	**Nunavut**	**NIHB**	**DND**	**VAC**	
$46.8742	$43.2020[a]	$43.2020[a]	$43.2020[a]	N/A	N/A	N/A	

DND = Department of National Defence; NIHB = Non-Insured Health Benefits Program; N/A = Price not available; VAC = Veterans Affairs Canada.

Note: All prices listed are formulary prices obtained from IQVIA DeltaPA unless otherwise noted.[9] Actual price paid by the plan may vary.

[a] Wholesale acquisition price from IQVIA DeltaPA.[9]

Table 25: Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate Price Variation Across CDR-Participating Drug Plans

Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate Prices in CDR-Participating Drug Plans ($)							
British Columbia	**Alberta**	**Saskatchewan**	**Manitoba**	**Ontario**	**New Brunswick**	**Nova Scotia**	**Prince Edward Island**
$43.2673[a]	$41.5740[a]	$41.9140	$44.1277[a]	$44.8643	$44.1143	$44.8643[a]	$44.8643[a]
Newfoundland and Labrador	**Yukon**	**Northwest Territories**	**Nunavut**	**NIHB**	**DND**	**VAC**	
$48.6778	$42.5303[a]	$42.5303[a]	$42.5303[a]	N/A	N/A	N/A	

DND = Department of National Defence; NIHB = Non-Insured Health Benefits Program; N/A = Price not available; VAC = Veterans Affairs Canada.

Note: All prices listed are formulary prices obtained from IQVIA DeltaPA unless otherwise noted.[9] Actual price paid by the plan may vary.

[a] Wholesale acquisition price from IQVIA DeltaPA.[9]

4. Discussion

4.1 Summary of Evidence

This submission for D/C/F/TAF FDC (Symtuza) was submitted as a new combination product based on the fact that DRV/COBI (Prezcobix) and FTC/TAF (Descovy) received a CDEC recommendation to reimburse with conditions in 2015 and 2016, respectively. Prezcobix is currently funded by a majority of the CDR-participating drug plans (Appendix 1).

D/C/F/TAF FDC is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents with no known mutations associated with resistance to the individual components of D/C/F/TAF.

In total, one phase II and two phase III studies[2-4] provide evidence of efficacy and safety of D/C/F/TAF FDC in the target population. The phase II study and AMBER were double-blind, while EMERALD was open-label. There were no major methodological issues for these three studies, although there are challenges in interpretation of results related to handling of missing data and potential bias in subgroup analysis. In addition, three phase I RCTs[11-13] evaluated the bioequivalence and bioavailability of D/C/F/TAF relative to the administration of its individual components (COBI-boosted DRV plus F/TAF FDC) in healthy volunteers.

4.2 Bioequivalence

The manufacturer's submission included a summary of one pivotal bioequivalence study[9] (TMC114FD2HTX1001 [N = 96 healthy men and women]) that compared the individual components of D/C/F/TAF with the individual components: DRV, F/TAF FDC, and COBI. A relative bioavailability study TMC114FD2HTX1002[12] assessed the impact of food on the PK of DRV, COBI, FTC, and TAF, administered as D/C/F/TAF FDC, compared with the combined administration of the separate drugs DRV + COBI + F/TAF. Another bioavailability study, GS-US-299-0101,[13] evaluated the PK and bioavailability of DRV, COBI, FTC, and TAF, administered as an STR, relative to the administration of the individual components in healthy volunteers.

The results of these studies suggested that the D/C/F/TAF 800 mg/150 mg/200 mg/10 mg FDC tablet is bioequivalent to combined administration of the separate drugs DRV, FTC/TAF FDC, and COBI in healthy volunteers. Furthermore, single doses of the D/C/F/TAF FDC were well tolerated in healthy volunteers.

4.3 Efficacy

The efficacy data provided in the manufacturer's submission were derived from one phase II RCT[2] and two phase III ongoing RCTs (AMBER[3] and EMERALD[4]) in adult patients with HIV-1 infection. Overall, the recruited patients had relatively mild disease and normal renal function. AMBER and EMERALD were ongoing studies not submitted to Health Canada because their data became available after the new drug submission.

Findings from the RCTs demonstrated that D/C/F/TAF FDC was noninferior to co-administration of the individual components of DRV, COBI, and F/TDF for virologic success in treatment-naive patients, up to week 48 of the treatment. Moreover, switching to D/C/F/TAF FDC was noninferior to remaining on treatment with bPI + F/TDF in terms of virologic rebound through 48 weeks in patients with virologic suppression. Resistance was evaluated in all three studies by genotyping. Comparisons between treatment groups were inconclusive because of the small number of patients included in the resistance analysis population for post-baseline mutations (eight, 14, and four patients from the phase II study, AMBER, and EMERALD, respectively).

4.4 Harms

Findings from the phase II RCT showed that the risk of treatment-emergent AEs was similar between D/C/F/TAF FDC (92%) and COBI-boosted DRV + F/TDF FDC (94%) in treatment-naive patients. SAEs were infrequent: 4.9% of patients in the D/C/F/TAF FDC group and 4% of patients in the control group reported an SAE during the study. AE leading to premature study drug discontinuation was reported in 1.9% of patients in the D/C/F/TAF group and 4% in the control group. The most frequently reported AEs for D/C/F/TAF included diarrhea (21.4%), upper respiratory tract infection (15.5%), fatigue (13.6%), nausea (12.6%), and rash (11.7%), which are consistent with the drug profile. Patients in the control group reported similar AEs.

In terms of AEs specifically related to the treatment, patients in the D/C/F/TAF group showed a better renal safety profile and less decline in BMD than those receiving DRV + COBI + F/TDF. According to the product monograph for D/C/F/TAF FDC, however,[5] the risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to administration of TAF cannot be excluded. The long-term bone health and future fracture risk are unknown, given the available data. The clinical expert expressed the concern about long-term use of TAF in adolescents due to its potential impact on bone development in this population.

Results of the two phase III ongoing RCTs also indicated that D/C/F/TAF FDC is well tolerated, and no new AEs were identified beyond the known AEs for the individual components of D/C/F/TAF.

Patients with hepatitis B or hepatitis C coinfection were excluded from all three RCTs. The Canadian product monograph for D/C/F/TAF has a black box warning stating that safety and efficacy have not been established in patients co-infected with HIV-1 and hepatitis B virus (HBV) and/or hepatitis C virus. Discontinuation of F + TAF (two of the components of the study drug) in patients co-infected with HBV and HIV-1 may be associated with severe acute exacerbations of hepatitis B.[[5]] The product monograph recommends that patients

co-infected with HIV-1 and HBV who discontinue D/C/F/TAF FDC should have clinical and laboratory monitoring for at least several months after treatment is discontinued. Similar warnings appear in the product monographs of many other FDC products approved in Canada, including those that contain FTC/TAF (i.e., Genvoya and Descovy),[14,15] FTC/TDF (i.e., Stribild, Truvada),[16,17] and lamivudine (Triumeq).[18]

4.5 Other Considerations

In the patient group input received for this submission, it was indicated that D/C/F/TAF FDC is a novel, once daily, FDC therapy featuring four drugs that are already on the Canadian market. The patient group emphasized the importance of patient adherence to the HIV therapy. Previous research has demonstrated that lower pill burden was associated with better adherence and virologic suppression.[19] High adherence rates (98% to 100%) were reported in the three included RCTs, and this can translate to lower drug-class resistance and more effective treatment.

4.6 Potential Place in Therapy[2]

D/C/F/TAF FDC is the first PI-containing STR, and the seventh STR to become available on the Canadian market (preceded by Atripla, Complera, Odefsey, Stribild, Genvoya, and Triumeq).

PI-based therapies have fallen out of favour in preference to those incorporating integrase nuclear strand transfer inhibitors or NNRTIs, because of the need for pharmacologic boosting through cytochrome P450 inhibition, side effects (diarrhea, worsening glucose intolerance, and dyslipidemia), and the lack of an STR formulation.

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. D/C/F/TAF FDC would offer another option in this patient group, but with little to recommend it over the other options.

There is a need for an STR for patients with past treatment failures and genotypic viral resistance. Darunavir is likely the most active PI against PI-resistant virus. However, the dose used in D/C/F/TAF FDC is not the one recommended for treatment of a resistant virus (600 mg twice daily); therefore, D/C/F/TAF FDC does not fulfill this need.

Still, D/C/F/TAF FDC 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. It may be less desirable for patients with diabetes mellitus or dyslipidemia, because of its propensity to aggravate these, which should be easily identifiable by the prescriber. The potential for drug interactions would restrict its use somewhat or require alterations of concomitant therapy. It would most likely be used for patients with HIV-1 infection already maintained on darunavir, either in the form of DRV/COBI or boosted by rtv. These patients are uncommon, as many would have been switched to an STR by now.

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

4.7 Cost

The manufacturer submitted a cost comparison of drug costs for D/C/F/TAF FDC versus its individual components, DRV/COBI and F/TAF. At the submitted daily price of $52.44, D/C/F/TAF FDC is at parity with the combined price of the available component medications. According to feedback from the clinical expert consulted by CADTH, there are a number of triple-therapy and quadruple-therapy STRs available on the market with similar indications, which should be considered as comparator treatments as well. The use of D/C/F/TAF FDC would present an additional cost per person per year in comparison to other available STRs, ranging from approximately $1,614 versus E/C/F/TDF to $10,869 versus efavirenz/lamivudine/TDF.

5. Conclusion

D/C/F/TAF FDC (Symtuza) is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with no known mutations associated with resistance to the individual components of D/C/F/TAF. The manufacturer's submission included a summary of three RCTs with a focus on the clinical efficacy and safety of D/C/F/TAF FDC in treatment-naive or treatment-experienced patients, and a summary of three bioequivalence/ bioavailability studies that demonstrated that D/C/F/TAF FDC has a comparable PK profile to that of its individual components (COBI-boosted DRV and F/TAF FDC).

The efficacy data provided in the manufacturer's submission were derived from one completed phase II study (GS-US-299-0102) and interim data from two ongoing phase III studies (AMBER and EMERALD). Virologic response (phase II study and AMBER) or virologic rebound (EMERALD) was the primary outcome measure in these studies. Study findings suggested that D/C/F/TAF FDC was noninferior to the co-administration of its individual components for virologic success in treatment-naive patients, at week 24 (phase II study) and week 48 (AMBER). In patients with virologic suppression resulting from prior ART with bPI + F/TDF, switching to D/C/F/TAF FDC was noninferior to remaining on previous ART for virologic rebound, at week 48 (EMERALD).

D/C/F/TAF FDC is well tolerated in general and has a safety profile similar to the co-administration of DRV + COBI + F/TDF FDC, or bPI + F/TDF FDC in the included studies. No new safety signals of D/C/F/TAF were identified beyond the known ADRs related to DRV + COBI + F/TDF FDC, DRV/COBI FDC, or bPI + F/TDF FDC.

Appendix 1: Drug Plan Listing Status for Individual Components

Table 26: Listing Status for Individual Components of the New Combination Product

Components	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Darunavir (Prezista)	RES	NB	RES	FB	FB	FB	FB	FB	RES	RES	FB	FB	RES	RES
Darunavir/ cobicistat (Prezcobix)	RES	NB	RES	NB	FB	RES	FB	FB	RES	RES	FB	FB	FB	RES
Cobicistat (Tybost)	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB
Emtricitabine (Emtriva)	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	RES
Emtricitabine/ tenofovir alafenamide (Descovy)	RES	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	FB
Tenofovir alafenamide	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB

AB = Alberta; BC = British Columbia; DND = Department of National Defence; FB = full benefit; MN = Manitoba; NB = not a benefit; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; RES = restricted benefit with specified criteria; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

Table 27: Restricted Benefit Criteria for Darunavir (Prezista) for the Treatment of HIV

Drug Plan	Criteria for Restricted Benefit
DND	Requests for special authorization are considered for members who are treatment-experienced and have demonstrated failure on multiple (2 or more) listed protease inhibitors OR are treatment-naive and protease inhibitor therapy is indicated.
VAC	Restricted infectious disease practitioners or providers who provide care to HIV patients.
Yukon	When prescribed by an infectious disease specialist.
Newfoundland and Labrador	• For use in treatment-experienced pediatric patients with HIV-1 infection. • For the treatment of HIV-1 in patients who are treatment-naive for whom a protease inhibitor therapy is indicated. • As an alternative protease inhibitor as part of a HIV treatment regimen for treatment-experienced adult patients who have demonstrated failure to multiple PIs and in whom less expensive PIs are not a treatment option.
Saskatchewan	a) For management of HIV disease. This drug, as with other antivirals in the treatment of HIV, should be used under the direction of an infectious disease specialist. b) When prescribed by, or on the advice of, an infectious disease specialist familiar with HIV treatment for post-exposure prophylaxis (PEP). Please refer to the HIV PEP Treatment document on the Formulary website.

DND = Department of National Defence; VAC = Veterans Affairs Canada.

Table 28: Restricted Benefit Criteria for Darunavir/Cobicistat (Prezcobix) for the Treatment of HIV

Drug Plan	Criteria for Restricted Benefit
Yukon	For the treatment of HIV infection in treatment-naive and treatment-experienced patients without darunavir resistance-associated mutations, when prescribed by an infectious disease specialist.
Newfoundland and Labrador	For treatment of HIV infection in treatment-naive and treatment-experienced patients without darunavir resistance-associated mutations. This drug, as with other antivirals in the treatment of HIV, should be used under the direction of an infectious disease specialist.
New Brunswick	For treatment of HIV infection in treatment-naive and treatment-experienced patients without darunavir resistance-associated mutations. Claim Note: Prescriptions written for beneficiaries of Plan U by NB infectious disease specialists and medical microbiologists experienced in treating patients with HIV/AIDS do not require special authorization.
Saskatchewan	For treatment of HIV infection in treatment-naive and treatment-experienced patients without darunavir resistance-associated mutations. This drug, as with other antivirals in the treatment of HIV, should be used under the direction of an infectious disease specialist.

Appendix 2: Summary of Patient Input

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

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

The Canadian Treatment Action Council (CTAC) is a national non-governmental organization addressing access to holistic treatment, care, and support for people living with HIV and hepatitis C (HCV). Its goals are to engage community members, service providers, policy-makers, and other relevant stakeholders to identify, develop, and implement policy and program solutions. Full CTAC membership is reserved for 1) individuals living with HIV (including HCV coinfection) and 2) organizations, groups, or projects with a substantial HIV mandate (including HCV coinfection).

CTAC declared that it did not receive help from outside the patient group to complete this submission, or to collect or analyze data used in this submission. It declared a financial payment from Gilead Sciences in excess of $50,000 within the last two years.

2. Condition-Related Information

Information was gathered via a national consultation webinar (on January 12, 2018) that provided an overview of the patient input process used by CADTH and reviewed the key findings from the darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) clinical trials. After the webinar, the attendees were sent a Web-based feedback survey link to gather additional information. Furthermore, social media was used to bring in those who had experience with any of the components of this four-drug combination or with the combination itself. Four male participants who identified themselves as HIV-positive attended the webinar. Three respondents were in their 50s, while the other was in his 40s. The respondents resided in Ontario, Manitoba, or Quebec. All of them are on treatment for HIV, and the number of years in treatment ranged from six years to approximately 20 years. The Symtuza submission was supplemented by the survey data that was collected by CTAC for the previous patient group input submissions for Descovy (F/TAF) and Genvoya (elvitegravir/C/F/TAF), and a concurrent patient submission for Juluca (dolutegravir/rilpivirine).

HIV is a serious, life-threatening disease that compromises a patient's immune system and, if left untreated, predisposes these patients to opportunistic infections. Highly active antiretroviral treatment (ART) is the mainstay for HIV management. In most cases, patients taking ART achieve viral suppression (an undetectable viral load) defined as less than 50 copies/mL in a blood sample. Hence, patients with HIV manage their disease as a chronic illness. However, patients with HIV often tend to experience "accelerated aging" and become more susceptible to inflammatory and non-infectious comorbidities such as cardiovascular, kidney, and liver disease, along with bone fractures. In addition to a number of disease-related complications, patients living with HIV often experience negative mental health outcomes. These can be due to the side effects from treatment or from social stigma, discrimination, and related stress. Mental health issues and stigma were noted by the respondents, including challenges encountered in the workplace and accessing the health care system: "Local doctors feel ill-equipped to treat HIV due to inexperience because of low patient caseloads with the condition. Stigma also play into it, I think. Unless they're familiar, doctors still see HIV as something more difficult to live with than it actually is." In 2011, the Canadian AIDS Society released a study that estimated a $1.3 million total economic loss per Canadian living with HIV. This includes a $670,000 average loss in labour productivity and a $380,000 average loss in quality of life.

Responses taken from the Juluca submission noted substantial impact on caregivers looking after patients living with HIV. One respondent highlighted that the challenges his/her spouse faces in providing support is surrounding 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 ability to acquire a social safety net.

3. Current Therapy-Related Information

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

Patients reported current or previous treatment experience with a variety of different treatments. None of the respondents to the Symtuza survey had experience with the D/C/F/TAF combination drug, although one indicated current or past use of regimens containing tenofovir/darunavir/emtricitabine. Treatments from all survey data combined in this submission ran the gamut from Prezista to Discovy, Intelence, Isentress, Norvir, Tivicay, and/or Atripla, with different combinations of these being used. Many respondents indicated that HIV treatment has resulted in noticeable improvements in their quality of life and their ability to participate in daily activities: “I am very healthy, employed, and also volunteering. Living life fully in a relationship and as a community member.” However, respondents from the dolutegravir/rilpivirine submission stated that staff time, funding, transportation, and other associated costs were barriers to providing support and had an impact on treatment adherence, mental health, and other determinants of health: “we have to decrease our direct support services, and in Prince Edward Island there are very little services for PHA’s in many areas, including addictions, mental health, housing and food securing, which put treatment lower on the priority list.” Other challenges presented from the HIV treatment included understanding stigma and its impact and navigating HIV-specific social services and institutional systems, including disability services, insurance, and mortgage.

4. Expectations About the Drug Being Reviewed

CTAC noted that D/C/F/TAF is a novel, once-daily, fixed-dose combination therapy featuring four drugs that are already on the Canadian market. Results of clinical trials of this drug suggested a favourable efficacy and safety profile. Its renal and bone benefits in ART-experienced patients were observed. One respondent who was currently on Atripla (tenofovir/emtricitabine/efavirenz) indicated that they would consider taking a D/C/F/TAF combination because of its ease of use and the potential better treatment effect of cobicistat and darunavir, while others expressed a reluctance to switch to this drug due to the adverse effects of FTC or because of the drug cost. Two of the four respondents felt the side effects of D/C/F/TAF were the same as their current regimen, and their quality of life using D/C/FTC/TAF would be equivalent to what they are experiencing on their current treatment.

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