Common Drug Review
Clinical Review Report

July 2015

Drug	darunavir/cobicistat (Prezcobix)
Indication	Used in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in treatment-naive and in treatment-experienced patients without darunavir (DRV) resistance-associated mutations (RAMs).
Listing request	As per indication.
Manufacturer	Janssen Inc.

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ABBREVIATIONS

ART	antiretroviral therapy
AZT	zidovudine
CDR	CADTH Common Drug Review
CI	confidence interval
COBI	cobicistat
HHS	US Department of Health and Human Services
DRV/COBI	cobicistat-boosted darunavir
DRV/r	ritonavir-boosted darunavir
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
HIV	human immunodeficiency virus
NRTI	nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
RAM	resistance-associated mutation
RNA	ribonucleic acid
RTV	ritonavir
TDF	tenofovir disoproxil fumarate
TLOVR	time to loss of virologic response

EXECUTIVE SUMMARY

Introduction

HIV attacks CD4+ T-cells, components of the immune system necessary for defending the body against infection. Left untreated, progressive impairment in immunity may lead to AIDS, the final stage of HIV where a patient can no longer fight off infections and certain malignancies. An estimated 71,300 people were living with HIV infection in Canada in 2011,[1] an increase of 11.4% from the 2008 estimate of 64,000. In 2013, there were 2,090 incident cases of HIV infection.

The current standard of care for HIV management is to treat with a combination of antiretroviral drugs with the primary goal of achieving and maintaining maximal suppression of viral load, leading to restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. Treatment adherence is an important predictor of the effectiveness of antiretroviral therapy (ART). It is associated with the degree of viral suppression and immunologic restoration achieved, time of progression of HIV infection to AIDS, and likelihood of death. Numerous options are available for ART. The choice of ART regimen for an individual patient must take into account drug potency, tolerability, convenience, and known or potential drug interactions, as well as comorbidities, ART history, concomitant medication use, and cost. The most commonly used regimens include three drugs consisting of two nucleotide or nucleoside reverse transcriptase inhibitors (N[t]RTIs) in combination with a drug from a different class, such as a protease inhibitor (PI).

Darunavir (DRV) is a PI that blocks the activity of the protease enzyme necessary for the assembly of HIV particles. Due to its rapid metabolism by cytochrome P450 3A (CYP 3A), DRV requires co-administration with CYP 3A inhibitors such as ritonavir (DRV/r) or cobicistat (DRV/COBI) due to its rapid metabolism by CYP 3A. DRV/r has previously been reviewed by the Canadian Expert Drug Advisory Committee for the treatment of treatment-experienced adult HIV-1 patients,[2] treatment-naive adult HIV-1 patients,[3] and treatment-experienced pediatric HIV-1 patients.[4] DRV received a recommendation for listing for all three patient populations. DRV/COBI 800 mg/150 mg, the focus of the current review, is now available as a single fixed-dose combination tablet. The Health Canada–approved indication for DRV/COBI is for use in combination with other antiretroviral drugs for the treatment of HIV in treatment-naive and treatment-experienced patients without DRV resistance-associated mutations (RAMs). The recommended oral dosing regimen is one tablet taken once daily with food.

Indication under review
Used in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in treatment-naive and in treatment-experienced patients without darunavir (DRV) resistance-associated mutations (RAMs).[a]
Listing criteria requested by sponsor
As per indication.

[a] The safety and efficacy of DRV/COBI has not been established in pediatric patients aged 18 years and younger.

The objective of this systematic review is to examine the beneficial and harmful effects of DRV/COBI 800 mg/150 mg for the treatment of HIV-1 infection in antiretroviral treatment-naive and treatment-experienced patients without DRV RAMs.

Results and Interpretation

Included Studies

The evidence for this review was drawn from one phase 3, 48-week, open-label, single-group study. GS-US-216-0130 (N = 314) evaluated the safety and efficacy of DRV/COBI 800 mg/150 mg as separate dosage forms administered in combination with two fully active nucleoside reverse transcriptase inhibitors (NRTIs) in treatment-naive (n = 296) and treatment-experienced (n = 18) HIV-1–infected patients with no DRV RAMs. Patients who completed 48 weeks of treatment were given the option to continue receiving open-label DRV/COBI 800 mg/150 mg in combination with NRTIs in an open-label rollover phase (no data from this phase were available). The primary efficacy end point of study GS-US-216-0130 was the proportion of patients with an HIV-1 ribonucleic acid (RNA) of less than 50 copies/mL at week 24 (Snapshot analysis). The primary end point was the proportion of patients experiencing at least one treatment-emergent Grade 3 (severe) or Grade 4 (life-threatening) adverse event through week 24.

The open-label, single-group design of study GS-US-216-0130 precluded an assessment of comparative effectiveness and safety versus other anti-HIV regimens, including DRV/r. With respect to generalizability, the enrolled population reflected a more advanced disease stage than what would be seen in clinical practice, with a lower proportion of Caucasian patients than what would be seen in Canada. As well, almost all (99%) of the treatment-naive patients in study GS-US-216-0130 were on a backbone regimen of emtricitabine/tenofovir, which is a higher proportion of patients than what would be seen in Canadian clinical practice. The treatment-experienced cohort was small (n = 18), limiting the generalizability of the overall study findings to this patient population.

Efficacy

In study GS-US-216-0130, the primary analysis of the proportion of treatment-naive patients achieving an HIV-1 RNA viral load suppression below 50 copies/mL using the Snapshot analysis with DRV/COBI 800 mg/100 mg was similar at week 24 (83.7%) and week 48 (82.7%). The proportion of treatment-naive patients with virologic failure was [redacted] at week 24 ([redacted]) and week 48 ([redacted]). The time to loss of virologic response analysis supported the findings from the Snapshot analysis. The treatment-experienced cohort consisted of 18 patients, limiting the data on the efficacy of DRV/COBI 800 mg/100 mg once daily for this patient population. As this was a single-group study, it is difficult to estimate with certainty the efficacy of DRV/COBI compared with placebo or other anti-HIV regimens. However, the results of study GS-US-216-0130 are generally consistent with those seen in the DRV/r trials in treatment-naive and treatment-experienced patients.

The manufacturer provided an adjusted comparative analysis to compare DRV/COBI 800 mg/150 mg once daily with DRV/r 800 mg/100 mg once daily, in which DRV/COBI was found to be non-inferior to DRV/r based on virologic response at 48 weeks. Due to concerns regarding: comparability between treatment groups and the effectiveness of adjustments made for potential confounders; lack of transparency in the analytical model; and use of non-standard methods for performing the indirect comparison; there was uncertainty with regard to the validity of the results of this analysis.

There were no data reported in study GS-US-216-0130 on health-related quality of life.

The manufacturer conducted one pharmacokinetic study (TMC114IFD1001) to demonstrate that the bioavailability of DRV 800 mg when boosted with COBI 150 mg was similar when boosted with ritonavir (RTV) 100 mg. Study TMC114IFD1001 found that the DRV C_{max} and the area under the curve (AUC_{24h}) parameters confirmed bioequivalence between the COBI and RTV groups, but the DRV C_{min} and C_{0h} parameters were lower in the COBI group compared with the RTV group. A second pharmacokinetic

study confirmed that DRV and COBI administered as a fixed-dose combination were bioequivalent to the two drugs administered separately.

Harms

No deaths were reported up to week 48 of study GS-US-216-0130. The incidence of adverse events in study GS-US-216-0130 was similar through week 24 and week 48. The most common adverse events were diarrhea, headache, nausea, rash, and upper respiratory tract infection. A total of 16 treatment-naive patients (5.1%) withdrew from study treatment due to an adverse event, with 6 patients withdrawing due to rash. There were no deaths reported until week 48.

Skin reactions were observed during the clinical development program for DRV.[5] In study GS-US-216-0130, skin and subcutaneous tissue disorders were reported in [redacted] patients. The clinical expert consulted for this review indicated that skin reactions with DRV are usually not a major concern and rarely lead to treatment discontinuation.

COBI has been known to inhibit creatinine tubular secretion and thereby increase serum creatinine levels.[6] In study GS-US-216-0130, there was a decrease from baseline in the estimated glomerular filtration rate at week 24 and week 48, with a concomitant increase from baseline in serum creatinine levels at week 24 and week 48. [redacted] patients experienced a renal or urinary disorder. The clinical expert consulted for this review did not expect these changes to cause concern, although patients would be monitored for renal function regularly.

The manufacturer's adjusted analysis comparing DRV/COBI with DRV/r did not assess safety outcomes; hence, the relative safety of the two regimens remains uncertain. In the patient group input received by the CADTH Common Drug Review on this submission, concerns were expressed regarding fatigue, high cholesterol, and gastrointestinal adverse effects. RTV was perceived to be associated with considerable gastrointestinal effects. Diarrhea and nausea occurred in a considerable proportion (> 20%) of patients in the GS-US-216-0130 study. Reported rates of diarrhea with DRV/r are 8% to 14% for diarrhea and 4% to 7% for nausea. While direct comparison of these figures with the DRV/COBI data is difficult, they do not suggest that DRV/COBI has better gastrointestinal tolerability than DRV/r.

Conclusions

In one phase 3, open-label, single-group study, DRV/COBI 800 mg/150 mg administered as single drugs was shown to achieve relatively high rates of viral load suppression (HIV-1 RNA < 50 copies/mL) in treatment-naive and treatment-experienced adult patients with HIV-1 infection, although data for the treatment-experienced population were limited, as only 18 such patients were enrolled in the trial. Efficacy results for both populations were broadly similar to those for DRV/r in previous studies, although definitive conclusions regarding comparative efficacy and safety could not be drawn without a direct comparative trial. There were no data available on quality-of-life outcomes. The most commonly reported adverse events included diarrhea, headache, nausea, and rash. Rash was the most common adverse event that led to treatment discontinuation in treatment-naive patients. Although serum creatinine levels increased from baseline, there were few renal-related adverse events.

Pharmacokinetic data demonstrated the bioequivalence of DRV/COBI 800 mg/150 mg versus DRV/r 800 mg/100 mg with respect to DRV maximum plasma concentrations and AUC_{24h} values, but DRV C_{min} and C_{0h} parameters were lower with COBI than with RTV. Bioequivalence was also demonstrated for the fixed-dose combination of DRV/COBI 800 mg/150 mg versus administration as single drugs.

TABLE 1: SUMMARY OF RESULTS

	Study GS-US-216-0130		
	DRV/COBI 800 mg/150 mg Plus 2 NRTIs		
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Virologic success at week 24 (Snapshot analysis)			
HIV-1 RNA < 50 copies/mL, n (%)	[redacted]	[redacted]	258 (82.4)
95% CI, %	[redacted]	[redacted]	[redacted]
Virologic success at week 48 (Snapshot analysis)			
HIV-1 RNA < 50 copies/mL, n (%)	[redacted]	[redacted]	253 (80.8)
95% CI, %	[redacted]	[redacted]	[redacted]
Virologic failure at week 24 (Snapshot analysis)			
Virologic failure, n (%)	[redacted]	[redacted]	36 (11.5)
HIV-1 RNA ≥ 50 copies/mL, n (%)	[redacted]	[redacted]	22 (7.0)
Virologic failure at week 48 (Snapshot analysis)			
Virologic failure, n (%)	[redacted]	[redacted]	33 (10.5)
HIV-1 RNA ≥ 50 copies/mL, n (%)	[redacted]	[redacted]	14 (4.5)
Harms at week 48, n (%)			
Death	0	0	0
AEs	–	–	286 (91.4)
SAEs	–	–	26 (8.3)
WDAEs	–	–	[redacted]
Notable harms at week 48, n (%)			
Hepatobiliary disorders	–	–	[redacted]
Metabolism and nutrition disorders	–	–	[redacted]
Nervous system disorders	–	–	[redacted]
Psychiatric disorders	–	–	[redacted]
Skin and subcutaneous tissue disorders	–	–	[redacted]

AE = adverse event; CI = confidence interval; DRV/COBI = cobicistat-boosted darunavir; NRTI = nucleoside reverse transcriptase inhibitor; RNA = ribonucleic acid; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report;[7] Tashima et al.;[8] Summary of Clinical Safety.[9]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Human immunodeficiency virus (HIV) attacks CD4+ T-cells, components of the immune system necessary for defending the body against infection.[10] HIV progressively impairs immune response and, if left untreated, may lead to acquired immunodeficiency syndrome (AIDS), the final stage of HIV where a patient can no longer fight off infections and certain malignancies. HIV is transmitted through bodily fluids, and can be passed from an infected individual to a healthy individual through unprotected sex and sharing of drug needles. An infected mother can also pass the virus to her baby during pregnancy, birth, or breastfeeding.

The estimated number of people living with HIV infection in Canada in 2011 was 71,300 (range: 58,600 to 84,000),[1] an increase of 11.4% from the 2008 estimate of 64,000. In 2013, there were 2,090 incident cases of HIV infection compared with 2,099 in 2012 and 2,307 in 2011. This represents the lowest number of new cases of HIV infection since reporting began in 1985.[11] In 2013, men who had sex with men accounted for 49.3% of all adults (≥ 15 years) having positive HIV test reports containing a known exposure category, followed by heterosexuals (29.6%), and injection drug users (12.8%).[11] As in previous years, Ontario had the highest number of incident cases (827) in 2013, followed by Quebec (453), Alberta (239), British Columbia (272), and Saskatchewan (126).[12]

1.2 Standards of Therapy

The current standard of care for HIV management is to treat with antiretroviral therapy (ART), with the primary goal of achieving and maintaining maximal suppression of viral load (VL), which leads to restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.[13] These results can be achieved by using effective ART regimens to suppress HIV replication so that plasma HIV RNA levels (VL) are below assay-detectable limits — usually less than 50 copies/mL. Virologic failure occurs when viral suppression to less than 50 copies/mL does not occur, or when the VL rises to, and remains above, 50 copies/mL after achieving suppression to less than 50 copies/mL.[13]

The choice of ART regimen for an individual patient must take into account drug potency, tolerability, convenience, and known or potential drug interactions, as well as comorbidities, ART history, concomitant medication use, and cost.

Available ART drugs are categorized into six classes according to mechanism of action: nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, chemokine coreceptor type 5 antagonists, and integrase strand transfer inhibitors. In general, clinical practice guidelines (such as those by the US Department of Health and Human Services [DHHS][13]) recommend use of ART regimens that include three drugs consisting of two NRTIs in combination with a drug from a different antiretroviral drug class.[13] This approach has been shown to increase efficacy and reduce the likelihood of developing drug resistance.[13] The most commonly used regimens include three drugs consisting of two NRTIs in combination with a drug from a different class. For many drugs in the PI class, adequate plasma levels cannot be achieved without co-administration of a booster (i.e., inhibitor of P450 CYP 3A metabolism) such as low-dose ritonavir (RTV) or cobicistat. The DHHS recommends tenofovir/emtricitabine (TDF/FTC) as the preferred NRTI backbone with efavirenz, ritonavir-boosted atazanavir, ritonavir-boosted darunavir

(DRV/r) or raltegravir as the third drug when initiating ART in treatment-naive individuals. Alternative NRTI backbone pairs include abacavir with lamivudine.[13]

The DHHS guidelines recommend that ART be initiated for all HIV-infected individuals regardless of CD4+ cell counts to reduce the risk of disease progression.[13] This recommendation is supported by growing evidence that uncontrolled viremia is associated with development of non-AIDS–defining diseases, including cardiovascular disease, kidney disease, liver disease, neurologic complications, and malignancies.[13] Some concerns about the early initiation of ART include possible complications related to extended cumulative exposure to ART, impaired adherence due to medication fatigue, earlier development of resistance, and cost.

Approximately 25% of patients receiving ART are not virologically suppressed.[13] Virologic failure is related to patient- (e.g., ART non-adherence) and regimen-related factors (e.g., medication intolerance).[13] If virologic failure persists despite correcting these factors, the ART regimen should be changed to avoid further development of resistance mutations.[13] Antiretroviral drug resistance is an important contributor to suboptimal VL suppression and virologic failure. Therefore, baseline genotypic and phenotypic HIV drug-resistance testing is recommended to inform selection of treatment strategies when initiating ART in treatment-naive patients.[13] Drug-resistance testing is also recommended for treatment-experienced patients who are not achieving or maintaining VL suppression.[13] ART-experienced patients with drug resistance who are experiencing virologic failure should receive a new regimen that includes at least two, and preferably three, drugs expected to have antiretroviral activity based on the patient's treatment history and drug-resistance testing results.[13]

1.3 Drug

Darunavir (DRV) is a PI that blocks the activity of the protease enzyme necessary for the assembly of HIV particles. Due to its rapid metabolism in the intestines and liver by cytochrome P450 (CYP) 3A, DRV requires co-administration of a booster such as low-dose RTV or cobicistat (COBI), a selective CYP3A inhibitor without intrinsic anti-HIV activity. Darunavir boosted with ritonavir (DRV/r) has previously been reviewed by the Canadian Expert Drug Advisory Committee for the treatment of treatment-experienced adult HIV-1 patients,[2] treatment-naive adult HIV-1 patients,[3] and treatment-experienced pediatric HIV-1 patients.[4] Darunavir received a recommendation for listing for all three patient populations. The focus of the current review is a fixed-dose combination (FDC) tablet of DRV/COBI 800 mg/150 mg. Of note, COBI is also used as a booster in Stribild, an FDC of elvitegravir, tenofovir, and emtricitabine.

The Health Canada–approved indication for DRV/COBI is for use in combination with other antiretroviral drugs for the treatment of HIV in treatment-naive and treatment-experienced patients without DRV resistance-associated mutations (RAMs). The recommended oral dosing regimen is one tablet taken once daily with food.

Indication under review
Used in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in treatment-naive and in treatment-experienced patients without darunavir (DRV) resistance-associated mutations (RAMs).[a]
Listing criteria requested by sponsor
As per indication.

[a] The safety and efficacy of DRV/COBI has not been established in pediatric patients aged 18 years and younger.

TABLE 2: KEY CHARACTERISTICS OF NNRTI-, PROTEASE INHIBITOR- (RITONAVIR-), AND INSTI-BASED REGIMENS

	NNRTI-Based	PI	INSTI-Based
Regimen(s)	Efavirenz/tenofovir/ emtricitabine (EFV/TDF/FTC)	Cobicistat-boosted darunavir + tenofovir/emtricitabine (DRV/COBI + TDF/FTC) Ritonavir-boosted atazanavir + tenofovir/emtricitabine (ATV/r + TDF/FTC) Ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC) Cobicistat-boosted darunavir + tenofovir/emtricitabine (DRV/COBI + TDF/FTC)	Dolutegravir + abacavir/lamivudine or tenofovir/emtricitabine (DTG + ABC/3TC or TDF/FTC) Raltegravir + abacavir/lamivudine or tenofovir/emtricitabine (RAL + ABC/3FT or TDF/FTC)
Mechanism of action	**N(t)RTI** (e.g., 3TC, ABC, TDF, FTC) and **NNRTI** (e.g., EFV): inhibit HIV reverse transcriptase to prevent early-cycle viral replication **PI** (e.g., ATV, DRV, ritonavir): inhibits HIV protease to prevent late-cycle viral replication **INSTI** (e.g., RAL): inhibits HIV integrase to prevent entry of viral DNA into host cell genome		
Indication[a]	**EFV/TDF/FTC**: alone as a complete regimen or in combination with other ARTs for the treatment of HIV infection in adults.	**ATV:** in combination with other ARTs for treatment of HIV infection. **DRV**: co-administered with 100 mg ritonavir and with other ARTs, for treatment of HIV infection. **DRV/COBI:** administered as an FDC, in combination with other ARTs, for the treatment of HIV infection in patients without DRV RAMs. **TDF/FTC**: in combination with other ARTs (e.g., NNRTIs, PIs) for the treatment of HIV infection in adults.	**DTG:** in combination with other antiretroviral drugs, DTG is indicated for the treatment of HIV infection in adults and children 12 years of age and older and weighing at least 40 kg. **RAL**: in combination with other ARTs for treatment of HIV infection in adult patients. **ABC/3TC:** indicated in antiretroviral combination therapy for the treatment of HIV infection in adults. **TDF/FTC**: in combination with other ARTs (e.g., NNRTIs, PIs) for the treatment of HIV infection in adults.
Route of administration	Oral		
Recommended dose	**EFV/TDF/FTC**: 600 mg/300 mg /200 mg once daily	**ATV/r + TDF/FTC:** ATV/r 300 mg/100 mg once daily; TDF/FTC 300 mg/200 mg once daily **DRV/r + TDF/FTC**: DRV/r 800 mg/100 mg once daily (treatment-naive) **or** DRV/r 600 mg/100 mg BID (treatment-experienced); TDF/FTC 300 mg/200 mg once daily	**DTG + ABC/3TC:** DTG 50 mg QD + ABC/3TC 600 mg/300 mg QD **or** DTG 50 mg once daily + TDF/FTC 300 mg/200 mg once daily **RAL + TDF/FTC**: RAL 400 mg BID + ABC/3TC 600 mg/300 mg QD **or** RAL 400 mg BID; TDF/FTC 300 mg/200 mg QD

	NNRTI-Based	PI	INSTI-Based
		DRV/COBI + TDF/FTC: DRV/COBI 800 mg/150 mg FDC once daily; TDF/FTC 300 mg/200 mg once daily	
Serious side effects/safety issues	**EFV/TDF/FTC:** Contraindicated: multiple drugs (e.g., voriconazole; ergot derivatives; midazolam, triazolam; pimozide) **TDF/FTC**: Lactic acidosis; severe hepatomegaly with steatosis (including fatal cases) have been reported with nucleoside analogues (e.g., TDF); safety and efficacy not established in patients co-infected with HBV and HIV; renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with TDF.	**ATV:** Contraindicated with drugs that are highly dependent on CYP3A4 and/or UGT1A for clearance **DRV**: Contraindications: severe (Child-Pugh Class C) hepatic insufficiency: drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis), including fatal cases, have been reported; drugs that are highly dependent on CYP3A4 for clearance. **TDF/FTC**: Lactic acidosis; severe hepatomegaly with steatosis (including fatal cases) have been reported with nucleoside analogues (e.g., TDF); safety and efficacy not established in patients co-infected with HBV and HIV; renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with TDF.	**DTG:** Hepatitis, hypersensitivity reactions, and IRS. **RAL**: Severe, potentially life-threatening, and fatal skin reactions have been reported (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis). Caution when used concurrently with strong inducers of UGT1A1 (e.g., rifampin). **ABC/3TC:** Serious and sometimes fatal hypersensitivity reactions have been associated with therapy with abacavir sulphate and other products containing abacavir. **TDF/FTC**: Lactic acidosis; severe hepatomegaly with steatosis (including fatal cases) have been reported with nucleoside analogues (e.g., TDF); safety and efficacy not established in patients co-infected with HBV and HIV; renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with TDF.

3TC = lamivudine; ABC = abacavir; ART = antiretroviral treatment; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; BID = twice daily; DRV = darunavir; DRV/COBI = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; IRS = immune reconstitution syndrome; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; N(t)RTI = nucleoside or nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; QD = once daily; RAL = raltegravir; RAM = resistance-associated mutation; TDF = tenofovir; UGT = uridine diphosphate glucuronosyltransferase.

[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of DRV/COBI 800 mg/150 mg FDC for the treatment of HIV infection in adults without DRV RAMs.

2.2 Methods

All studies identified by Health Canada as pivotal trials for DRV/COBI FDC were included in the systematic review. Other studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Treatment-naive or treatment-experienced HIV-1 infected adults (18 years of age or older) without DRV RAMs	
Intervention	DRV/COBI 800 mg/150 mg FDC (or as separate dosage forms) administered orally once daily in combination with other ARTs	
Comparators	**Treatment-naive** NNRTI-based regimens: • EFV/TDF/FTC • EFV + ABC/3TC • RPV/TDF/FTC INSTI-based regimens: • DTG + TDF/FTC • DTG + ABC/3TC • RAL + TDF/FTC • RAL + ABC/3TC • EVG/COBI/TDF/FTC PI-based regimens: • ATV/r + TDF/FTC • ATV/r + ABC/3TC • DRV/r + TDF/FTC • DRV/r + ABC/3TC	**Treatment-experienced** RAL + OBT PI + OBT
Outcomes	**Key efficacy outcomes** • Percentage of patients with VL < 50 copies/mL at end of trial (Snapshot or TLOVR analyses) • Percentage of patients with VL > 50 copies/mL at end of trial • Reduction of $\log_{10}$ VL from baseline • Change in CD4+ cell count from baseline **Other efficacy outcomes** • Morbidity • Mortality • Development of resistance mutations • Patient adherence/persistence • Quality of life by validated scale **Harms outcomes** • AEs, SAEs, WDAEs	

	Notable harms Metabolic complications (e.g., changes in blood lipids, glucose) Liver complications Renal complications Skin reactions (e.g., rash) CNS/cognitive effects (e.g., headache, fatigue, nausea, insomnia, dizziness, depression, anxiety)
Study Design	Published and unpublished double-blind RCTs

3TC = lamivudine; ABC = abacavir; AE = adverse event; ART = antiretroviral therapy; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; CNS = central nervous system; COBI = cobicistat; DRV/COBI = cobicistat-boosted darunavir; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; IRS = immune reconstitution syndrome; N(t)RTI = nucleoside or nucleotide reverse transcriptase inhibitor; OBT = optimized background therapy; PI = protease inhibitor; RAL = raltegravir; RAM = resistance-associated mutation; RCT = randomized controlled trial; RPV = rilpivirine; SAE = serious adverse event; TDF = tenofovir; TLOVR = time to loss of virologic response; VL = viral load; WDAE = withdrawal due to adverse event.

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concepts were: Prezcobix OR (Darunavir OR Prezista OR DRV OR TMC 114 OR TMC 41629) AND (Cobicistat OR Tybost OR GS 9350).

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

The initial search was completed on October 28, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on March 18, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (hwww.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free) and Internet Search. Google and other Internet search engines were used to search for additional Web-based materials.

These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

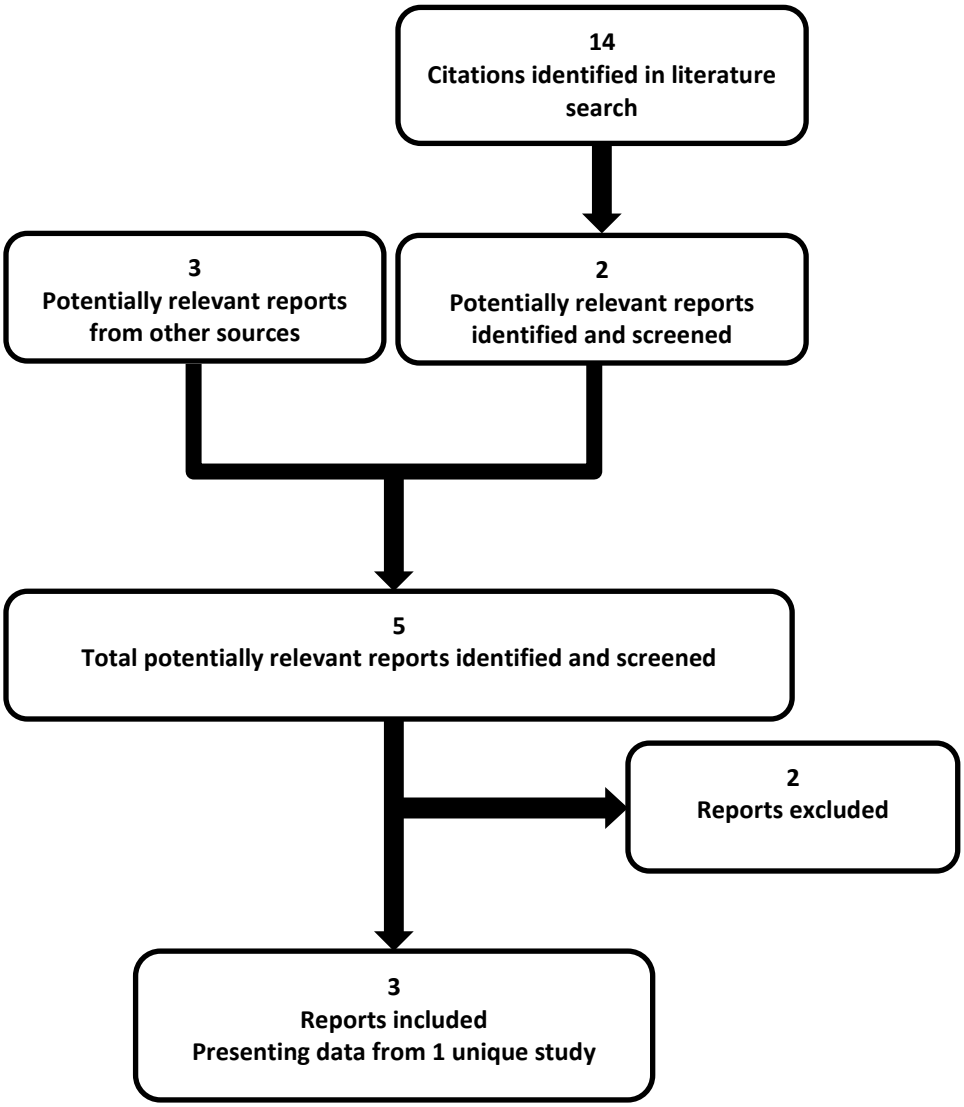


TABLE 4: DETAILS OF INCLUDED STUDY

		Study GS-US-216-0130
Designs and Populations	**Study design**	Open-label single-group study
	Locations	56 study centres in the United States
	Enrolled (N)	314 (296 treatment-naive; 18 treatment-experienced)
	Inclusion criteria	• HIV-1 infected adults ≥ 18 years • Plasma HIV-1 RNA ≥ 1,000 copies/mL at screening • Negative for DRV RAMs • Treatment-naive: no prior use of any approved or investigational ARV drug for any length of time • Treatment-experienced: stable ARV regimen for ≥ 12 weeks prior to screening
	Exclusion criteria	• Pregnant or breastfeeding women • Acute hepatitis 30 days prior to study entry • Malignancy within the last 5 years other than Kaposi sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma • Serious infection that required parenteral antibiotics or antifungal therapy 30 days prior to baseline • History of decompensated cirrhosis • Abnormal hepatic transaminase levels (> 2.5 ULN) or bilirubin levels (> 1.5 mg/dL) • Inadequate renal function (eGFR < 80 mL/min) • Receiving drug treatment for HCV
Drugs	**Intervention**	• DRV 800 mg (2 × 400 mg tablets QD with food) + COBI 150 mg (1 × 150 mg tablet QD with food), plus • 2 NRTIs based on resistance testing at screening (for patients with an M184V/I reverse transcriptase mutation; FTC or 3TC could be included as a third NRTI)
	Comparator(s)	None
Duration	**Phase**	
	OL phase	48 weeks
	OL rollover study	Patients who completed 48 weeks of treatment were given the option to receive open-label DRV/COBI + NRTIs and attend study visits every 12 weeks until the investigational product becomes commercially available. [redacted]
Outcomes	**Primary end point**	• Safety: Proportion of patients experiencing at least one treatment-emergent Grade 3 (severe) or Grade 4 (life-threatening) AE through week 24
	Other end points	• Proportion of patients with HIV-1 RNA < 50 copies/mL at week 24 (Snapshot analysis) • Proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 (Snapshot analysis) • Proportion of patients who achieved and maintained HIV-1 RNA < 50 copies/mL through week 24 and week 48 (TLOVR analysis) • Change from baseline in plasma HIV-1 RNA • Change from baseline in CD4+ cell count • Development of resistance mutations
Notes	**Publications**	Tashima et al.[8]

3TC = lamivudine; AE = adverse event; ARV = antiretroviral; COBI = cobicistat; DRV = darunavir; DRV/COBI = cobicistat-boosted darunavir; eGFR = estimated glomerular filtration rate; FTC = emtricitabine; HCV = hepatitis C virus; NRTI = nucleoside reverse transcriptase inhibitor; OL = open label; QD = once daily; RAM = resistance-associated mutation; RNA = ribonucleic acid; TLOVR = time to loss of virologic response; ULN = upper limit of normal.
Note: one additional report was included: Health Canada Reviewer's Report.[14]
Source: Clinical Study Report[7] and CADTH Common Drug Review submission.[15]

3.2 Included Studies

3.2.1 Description of Studies

One phase 3, 48-week, open-label, single-group pivotal study was included in this systematic review. GS-US-216-0130 (N = 314) evaluated the safety and efficacy of DRV/COBI 800 mg/150 mg administered as separate dosage forms in combination with two fully active NRTIs in treatment-naive (n = 296) and treatment-experienced (n = 18) patients infected with HIV-1 with no DRV RAMs. Patients who completed 48 weeks of treatment were given the option to continue receiving open-label DRV/COBI 800 mg/150 mg in combination with NRTIs in the open-label rollover phase (no data presented). Safety and efficacy data for week 24 and week 48 are presented.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

HIV-infected patients aged 18 years or older with a plasma HIV-1 RNA level of at least 1,000 copies/mL and no DRV RAMs (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, or L89V) were eligible for inclusion in study GS-US-216-0130. Both treatment-naive and treatment-experienced patients were included. Treatment-experienced patients needed to be on a stable antiretroviral regimen for at least 12 weeks prior to screening. The number of previous regimens received was not reported.

Patients were excluded if they had acute hepatitis 30 days prior to study entry or were receiving drug treatment for hepatitis C virus. Patients were also excluded if they had inadequate renal function as determined by glomerular filtration rate or abnormal liver function as determined by hepatic transaminase levels and bilirubin levels.

b) Baseline Characteristics

The majority of patients were male (89.1%) and Caucasian (59.7%), with a mean age of 36 years (Table 5). Treatment-naive patients had a mean CD4+ cell count of 378.2/µL, while treatment-experienced patients had a mean CD4+ cell count of 197.8/µL. The majority of patients had asymptomatic HIV infection, and approximately half had a baseline HIV-1 RNA VL of ≤ 100,000 copies/mL, with a mean of 4.8 $\log_{10}$ copies/mL. The most common risk factor for HIV transmission was homosexual sex. A small proportion of patients were co-infected with hepatitis B (1.6%) or hepatitis C (2.6%). Previous treatments received by patients in the treatment-experienced cohort were not reported.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Criteria	Study GS-US-216-0130		
	DRV/COBI 800 mg/150 mg + 2 NRTIs		
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Mean age, years (SD)	36 (10.3)	45 (10.9)	36 (10.6)
Male sex, n (%)	266 (90.2)	13 (72.2)	279 (89.1)
Mean BMI, kg/m^2 (SD)	[redacted]	[redacted]	[redacted]
Race, n (%)			
Caucasian	176 (59.7)	11 (61.1)	187 (59.7)
Black or African heritage	101 (34.2)	7 (38.9)	108 (34.5)
Disease characteristics			
Mean time since HIV diagnosis, years (SD)	[redacted]	[redacted]	[redacted]
Mean HIV-1 RNA, $\log_{10}$ copies/mL (SD)	[redacted]	[redacted]	[redacted]

Criteria	Study GS-US-216-0130		
	DRV/COBI 800 mg/150 mg + 2 NRTIs		
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
HIV RNA category (copies/mL), n (%)			
≤ 100,000 copies/mL	173 (58.6)	9 (50.0)	182 (58.1)
> 100,000 copies/mL	122 (41.4)	9 (50.0)	131 (41.9)
Mean CD4+ cell count, cells/mm^3 (SD)	378.2 (199.9)	197.8 (214.3)	367.8 (204.8)
CD4+ cell count category (cells/µL), n (%)			
≤ 50	[redacted]	[redacted]	[redacted]
51 to ≤ 200	[redacted]	[redacted]	[redacted]
201 to ≤ 350	[redacted]	[redacted]	[redacted]
351 to ≤ 500	[redacted]	[redacted]	[redacted]
> 500	[redacted]	[redacted]	[redacted]
HIV disease status			
Asymptomatic	241 (81.7)	10 (55.6)	251 (80.2)
Symptomatic	[redacted]	[redacted]	[redacted]
AIDS	[redacted]	[redacted]	[redacted]
HIV risk factors			
Heterosexual sex	[redacted]	[redacted]	[redacted]
Homosexual sex	[redacted]	[redacted]	[redacted]
IV drug use	[redacted]	[redacted]	[redacted]
Positive HBV surface antigen, n (%)	5 (1.7)	0	5 (1.6)
Positive HCV surface antigen, n (%)	7 (2.4)	1 (5.6)	8 (2.6)

BMI = body mass index; DRV/COBI = cobicistat-boosted darunavir; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; NA = not applicable; NRTI = nucleoside reverse transcriptase inhibitor; RNA = ribonucleic acid; SD = standard deviation.
Source: Clinical Study Report.[7]

3.2.3 Interventions

Patients took DRV 800 mg (two 400 mg tablets) and COBI 150 mg (one 150 mg tablet) once daily with food in combination with two investigator-selected NRTIs that were determined based on resistance testing at screening. A total of 99.0% of treatment-naive patients and [redacted] of treatment-experienced patients were on a background regiment of emtricitabine/tenofovir (FTC/TDF). Patients with the M184V/I reverse transcriptase mutation present at screening could receive emtricitabine or lamivudine as a third NRTI for the purpose of maintaining the M184V/I mutation.

Patients and investigators were discouraged from changing components of the study regimen during the study, and changes were permitted only for the management of confirmed suboptimal virologic response. Patients were counselled regarding the importance of adherence to their treatment regimen and of taking their study medication at approximately the same time each day.

3.2.4 Outcomes

a) Efficacy

The primary efficacy outcome in study GS-US-216-0130 was the proportion of patients with HIV-1 RNA levels of less than 50 copies/mL at week 24 as defined by the US Food and Drug Administration (FDA)

Snapshot analysis. This analysis uses HIV-1 RNA data at the time point of interest. This outcome was also analyzed at week 48 as a secondary efficacy outcome. Patient virologic outcome was defined according to the following categories:

- **Virologic success**: patients whose last available HIV-1 RNA value was less than 50 copies/mL in the analysis window while on treatment.
- **Virologic failure**: patients whose last available HIV-1 RNA value was 50 copies/mL or higher in the analysis window while on treatment. Virologic failure also included patients or who did not have any on-treatment HIV-1 RNA data in the analysis window (because of lack of efficacy or a reason other than an adverse event, death, or lack of efficacy), and whose last available HIV-1 RNA value on treatment was 50 copies/mL or higher.
- **No virologic data in the analysis window**: patients who had discontinued treatment prior to or within the analysis window because of: an adverse event or death; a reason other than an adverse event, death, or lack of efficacy (and their last available HIV-1 RNA value on treatment was less than 50 copies/mL); or they had missing data during the window, but remained on study drugs.

A secondary efficacy outcome was the proportion of patients who achieved and maintained an HIV-1 RNA of less than 50 copies/mL through week 24 and week 48 using the FDA-defined time to loss of virologic response (TLOVR) algorithm, which incorporates longitudinal data to assess confirmed virologic response at various time points across the study period.[16] In this analysis, the earliest occurrence of any of the following events was recorded as the time to loss of response:

[redacted]

Other secondary efficacy outcomes in study GS-US-216-0130 included the following:

- Change from baseline in plasma HIV-1 RNA VL over time
- Change from baseline in CD4+ cell count over time.

Harms

The primary end point was the proportion of patients experiencing at least one treatment-emergent Grade 3 (severe) or Grade 4 (life-threatening) adverse event through week 24. Safety data (adverse events, serious adverse events, withdrawals due to adverse events) were presented through week 24 and week 48.

3.2.5 Statistical Analysis

a) Sample Size Calculation

A sample size of 300 patients was planned to provide a 95% chance of observing at least one adverse event if the true incident rate of the event was 1%. This sample size resulted in a two-sided confidence interval (CI) with 95% limits at ± 0.047, assuming a virologic response rate of 80% (i.e., 95% CI: 80% ± 4.7%).

b) Missing Data

Missing data were not imputed for the primary safety and efficacy evaluations.

c) Analysis Populations

All patients who were enrolled in the study and received at least one dose of both study medications (DRV and COBI) were included in the full analysis set, which was the primary analysis set for the safety and efficacy end points.

3.3 Patient Disposition

The disposition of patients in study GS-US-216-0130 is presented in Table 6. A total of 397 patients were screened, with 314 patients enrolled. The majority of screening failures were due to an estimated glomerular filtration rate of less than 80 mL/min, or a VL of less than 1,000 HIV-1 RNA copies/mL. A total of 313 enrolled patients received at least one dose of DRV and COBI. Of these, 295 were treatment-naive and 18 were treatment-experienced. Overall, 45 (14.4%) patients discontinued from the study drug by week 48. No patients who were treatment-experienced upon enrolment discontinued from the study drug due to an adverse event, while 15 (5.1%) treatment-naive patients discontinued from the study drug due to an adverse event.

TABLE 6: PATIENT DISPOSITION

Criteria, N (%)	Study GS-US-216-0130		
	DRV/COBI 800 mg/150 mg + 2 NRTIs		
	Treatment-Naive	Treatment-Experienced	Total
Screened	361	36	397
Enrolled	296	18	314
Full analysis set	295 (100)	18 (100)	313 (100)
Discontinued from study drug by week 24	36 (12.2)	3 (16.7)	39 (12.5)
Adverse event	15 (5.1)	0	15 (4.8)
Lost to follow-up	[redacted]	[redacted]	[redacted]
Patient non-compliance	[redacted]	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]	[redacted]
Investigator's discretion	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]
Discontinued from study drug by week 48	NR	NR	45 (14.4)
Adverse event	NR	NR	15 (4.8)
Lost to follow-up	NR	NR	13 (4.2)
Withdrew consent	NR	NR	7 (2.2)
Patient non-compliance	NR	NR	6 (1.9)
Investigator's discretion	NR	NR	2 (0.6)
Protocol violation	NR	NR	2 (0.6)

DRV/COBI = cobicistat-boosted darunavir; NRTI = nucleoside reverse transcriptase inhibitor; NR = not reported.
Source: Clinical Study Report;[7] Tashima et al.[8]

3.4 Exposure to Study Treatments

Study drug adherence was measured by the number of pills taken divided by the number of pills prescribed. Study drug adherence rates for DRV plus COBI at week 24 and week 48 are presented in Table 7. At week 24 and week 48, a greater proportion of patients in the treatment-naive group had an adherence rate of at least 90% compared with the treatment-experienced group ([redacted]).

The majority of patients (99.0% of treatment-naive; [redacted] of treatment-experienced) received an FDC of emtricitabine (FTC) 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg, as the background regimen (Table 8).

TABLE 7: STUDY DRUG ADHERENCE TO DARUNAVIR PLUS COBICISTAT AT WEEK 24 AND WEEK 48

Study Drug Adherence, %	Study GS-US-216-0130		
	DRV/COBI 800 mg/150 mg + 2 NRTIs		
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Week 24			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Patients with ≥ 90% adherence, n (%)	[redacted]	[redacted]	[redacted]
Patients with ≥ 95% adherence, n (%)	[redacted]	[redacted]	[redacted]
Week 48			
Mean (SD)	NR	NR	NR
Median (range)	100 (NR)	100 (NR)	100 (NR)
Patients with ≥ 90% adherence, n (%)[a]	283 (95.9)	16 (88.9)	299 (95.5)

DRV/COBI = cobicistat-boosted darunavir; NR = not reported; NRTI = nucleoside reverse transcriptase inhibitor; SD = standard deviation.
[a] Data for ≥ 95% adherence at week 48 not reported.
Source: Clinical Study Report;[7] Tashima et al.[8]

TABLE 8: BACKGROUND NRTIS RECEIVED DURING THE STUDY

Background Regimen	Study GS-US-216-0130		
	DRV/COBI 800 mg/150 mg + 2 NRTIs		
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
FTC/TDF	[redacted]	[redacted]	[redacted]
AZT + FTC/TDF	[redacted]	[redacted]	[redacted]
ABC + TDF	2 (0.7)	1 (5.6)	3 (1.0)
ABC + FTC/TDF	[redacted]	[redacted]	[redacted]
ABC/3TC	1 (0.3)	0	1 (0.3)
DDI + FTC	0	1 (5.6)	1 (0.3)

3TC = lamivudine; ABC = abacavir; AZT = zidovudine; DDI = didanosine; DRV/COBI = cobicistat-boosted darunavir; FTC = emtricitabine; NRTI = nucleoside reverse transcriptase inhibitor; TDF = tenofovir disoproxil fumarate.
Source: Clinical Study Report.[7]

3.5 Critical Appraisal

3.5.1 Internal Validity

Study GS-US-216-0130 was an open-label, single-group study with no comparator group. This study was conducted in a manner similar to previous HIV-1 studies using well-established end points, but the lack of a comparator group makes it difficult to quantify the comparative efficacy and safety of DRV/COBI 800 mg/150 mg and other regimens. In particular, a non-inferiority randomized controlled trial comparing DRV/COBI with ritonavir-boosted DRV would have been valuable in confirming the therapeutic equivalence of these regimens.

The primary end point for the study was the proportion of patients experiencing Grade 3 and Grade 4 adverse events, the classification of which may be subjective. Furthermore, knowledge on the part of the investigators regarding the safety profile of DRV, COBI, or the backbone therapy could have resulted in bias in terms of what adverse events were recorded or attributed to therapy. In addition, the true number of adverse events may have been under-represented due to missing data.

3.5.2 External Validity

The baseline characteristics of the patients enrolled in study GS-US-216-0130 reflected a more advanced disease stage, with 41.9% of patients having HIV-1 RNA levels of more than 100,000 copies/mL. According to the clinical expert consulted for this review, this level is higher than what would be seen in clinical practice. The clinical expert noted there would be a higher proportion of Caucasian patients encountered in the Canadian context than what was seen in the study (59.7%), although this aspect is unlikely to have an impact on the observed efficacy of DRV/COBI. In addition, few patients enrolled in study GS-US-216-0130 were treatment-experienced (n = 18), limiting the amount of data on the efficacy and safety of DRV/COBI 800 mg/150 mg for this patient population.

The majority of treatment-naive patients (99.0%) were on a background regimen of FTC/TDF. The clinical expert consulted for this review indicated this was a higher proportion than what would be seen in clinical practice for treatment-naive HIV-1 patients in Canada. In addition, the backbone regimen of AZT + FTC/TDF that was used by [redacted] treatment-experienced patients is not used in current Canadian clinical practice due to its relatively poor tolerability.

DRV/COBI 800 mg/150 mg is approved as a single-tablet FDC, but this study administered both DRV and COBI as separate drugs. It is unclear from this study whether this would have an effect on efficacy and safety outcomes, and whether this would impact adherence rates. However, adherence rates were already quite high in the trial, and a single-tablet regimen is expected to have at least the same level of adherence. As well, the manufacturer demonstrated that administration of DRV/COBI 800 mg/150 mg as individual drugs was bioequivalent to the FDC tablet (see APPENDIX 5).

There was a lack of data on the safety and efficacy of DRV/COBI 800 mg/150 mg in the pediatric population.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (section 2.2, Table 3) are reported subsequently.(APPENDIX 4 for detailed efficacy data.)

3.6.1 Virologic Outcomes

a) Viral Load Under 50 Copies/mL (Snapshot Analysis)

The proportion of patients who achieved a VL of less than 50 copies/mL at week 24 was 83.7% (247 out of 295) in the treatment-naive cohort and 61.1% (11 out of 18) in the treatment-experienced cohort (Table 9 and Table 11). The proportion of patients with virologic failure at week 24 was [redacted] in the treatment-naive cohort and [redacted] in the treatment-experienced cohort, with [redacted] of treatment-naive patients and [redacted] of treatment-experienced patients having an HIV-1 RNA VL of ≥ 50 copies/mL. The remaining patients with virologic failure discontinued study drug due to reasons other than lack of efficacy and had a last-available HIV-1 RNA of ≥ 50 copies/mL. The proportion of patients with no virologic data in the week 24 window was [redacted] in the treatment-naive cohort. [redacted] were missing virologic data at week 24 in the treatment-experienced cohort.

Similar results were seen at week 48, with 82.7% (244 out of 295 patients) and 50.0% (9 out of 18) achieving a VL of less than 50 copies/mL in the treatment-naive and treatment-experienced cohorts, respectively. The proportion of patients with virologic failure at week 48 was [redacted] in the treatment-naive cohort and [redacted] in the treatment-experienced cohort. The proportion of patients with no virologic data in the week 48 window was 9.2% (27 out of 295) in the treatment-naive cohort. No patients were missing virologic data at week 48 in the treatment-experienced cohort.

b) Viral Load Under 50 Copies/mL (Time to Loss of Virologic Response Analysis)

Similar results were seen in the TLOVR analysis as in the Snapshot analysis. The proportion of patients who achieved a VL of less than 50 copies/mL at week 24 was [redacted] in the treatment-naive cohort and [redacted] in the treatment-experienced cohort (Table 9 and Table 12). The proportion of patients with virologic failure at week 24 was [redacted] in the treatment-naive cohort and [redacted] in the treatment-experienced cohort, with [redacted] of treatment-naive patients and [redacted] of treatment-experienced patients never having been suppressed through week 24. [redacted] in the treatment-naive cohort experienced viral rebound through week 24. The proportion of patients who discontinued from treatment prior to the week 24 analysis window was [redacted] in the treatment-naive cohort and [redacted] in the treatment-experienced cohort.

At week 48, the proportion of patients who achieved a VL of less than 50 copies/mL was 83.1% (245 out of 295) in the treatment-naive cohort and 44.4% (8 out of 18) in the treatment-experienced cohort. The proportion of patients with virologic failure at week 48 was [redacted] in the treatment-naive cohort and [redacted] in the treatment-experienced cohort, with [redacted] of treatment-naive patients and [redacted] of treatment-experienced patients never having been suppressed through week 48. [redacted] in the treatment-naive cohort and [redacted] in the treatment-experienced cohort experienced viral rebound through week 48. The proportion of patients who discontinued from treatment prior to the week 48 analysis window was [redacted] in the treatment-naive cohort and [redacted] in the treatment-experienced cohort.

c) Change from Baseline in Plasma HIV-1 RNA

The mean (standard deviation [SD]) decrease in $\log_{10}$ VL from baseline was [redacted] at week 24 and [redacted] at week 48 in treatment-naive patients (Table 13). In treatment-experienced patients, the mean (SD) decrease was [redacted] at week 24 and [redacted] at week 48. A graphical representation of the mean change in $\log_{10}$ VL from baseline over time until week 48 for the treatment-naive cohort is presented in Figure 2. [redacted]
Also shown in Figure 2 for the purpose of comparison is the mean change in $\log_{10}$ VL from baseline to week 48 for the ARTEMIS DRV/r group. ARTEMIS was a randomized, active-controlled, open-label study comparing DRV/r 800 mg/100 mg once daily with ritonavir-boosted lopinavir (LPV/r) 800 mg/200 mg once daily in treatment-naive patients.

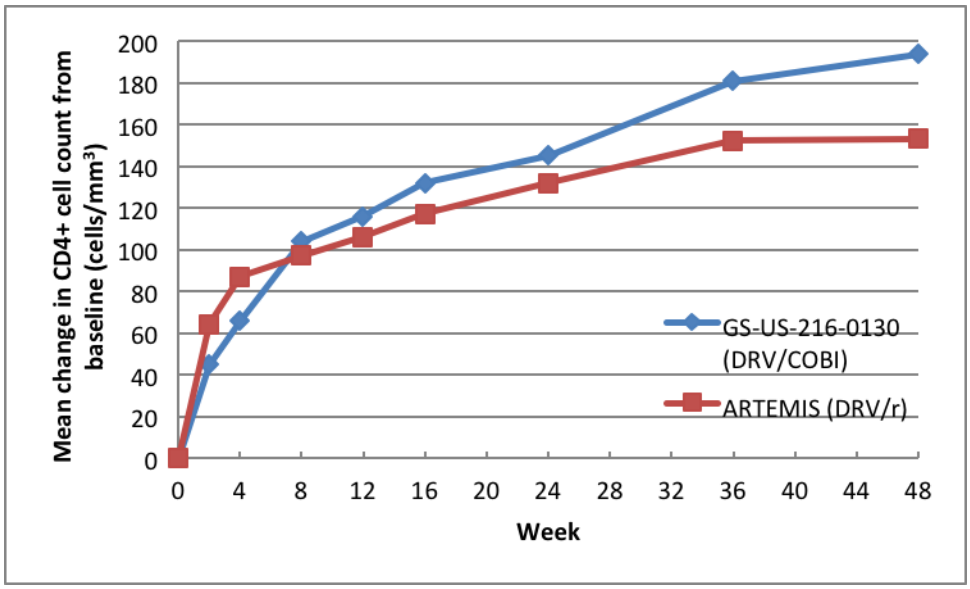
FIGURE 2: MEAN CHANGE IN $\log_{10}$ VIRAL LOAD FROM BASELINE OVER TIME IN STUDY GS-US-216-0130 AND ARTEMIS IN TREATMENT-NAIVE PATIENTS

Confidential figure removed at manufacturer's request

3.6.2 Change From Baseline in CD4+ Cell Count

Mean baseline CD4+ cell counts were higher in the treatment-naive cohort than in the treatment-experienced cohort (378 cells/µL versus 198 cells/µL) (Table 14). The mean (SD) increase from baseline in CD4+ cell count was 145 (131.6) cells/µL at week 24 and 194 (152.1) cells/µL at week 48 in treatment-naive patients. In treatment-experienced patients, the mean (SD) increase was 99 (161.9) cells/µL at week 24 and 121 (157.0) cells/µL at week 48. A graphical representation of the mean change in CD4+ cell count from baseline over time until week 48 for the treatment-naive cohort is presented in Figure 3, along with analogous results from the ARTEMIS trial's DRV/r 800 mg/100 mg once-daily group.

FIGURE 3: MEAN CHANGE IN CD4+ CELL COUNT FROM BASELINE OVER TIME IN STUDY GS-US-216-0130 AND ARTEMIS IN TREATMENT-NAIVE PATIENTS



DRV/COBI = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir.

3.6.3 Development of Resistance Mutations

The resistance analysis population was comprised of patients who, while receiving ART, achieved a suboptimal virologic response (i.e., HIV-1 RNA VL of ≥ 50 copies/mL **and** a < 1 $\log_{10}$ reduction from baseline at week 8 and confirmed at next visit), or experienced a virologic rebound (i.e., HIV-1 RNA of ≥ 400 copies/mL on two subsequent visits after an initial virologic suppression of < 50 copies/mL **or** > 1 $\log_{10}$ increase in HIV-1 RNA from nadir on two subsequent visits).

At week 48, the resistance analysis population consisted of 15 patients: [redacted] were treatment-naive and [redacted] were treatment-experienced (Table 15). One treatment-experienced patient developed a resistance mutation to darunavir as a mixture with wild-type (I84I/V). However, this mutation was not associated with phenotypic resistance to darunavir or other PI. One treatment-experienced patient showed transient development of the L741I/L and P225H/P NRTI resistance mutations prior to week 24, but these mutations were not detected at week 48. One treatment-naive patient and one treatment-experienced patient developed M184V NRTI resistance mutations while receiving FTC.

3.6.4 Other Efficacy Outcomes

HIV-related morbidity and quality of life were not reported in study GS-US-216-0130. Deaths occurring in the study are described under Harms (section 3.7).

TABLE 9: KEY EFFICACY OUTCOMES

	Study GS-US-216-0130		
	DRV/COBI 800 mg/150 mg + 2 NRTIs		
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Virologic success at week 24 (Snapshot analysis)			
HIV-1 RNA < 50 copies/mL	247 (83.7)	11 (61.1)	258 (82.4)
95% CI	79.0 to 87.8	[redacted]	77.8 to 86.5
Virologic success at week 48 (Snapshot analysis)			
HIV-1 RNA < 50 copies/mL	244 (82.7)	9 (50.0)	253 (80.8)
95% CI	[redacted]	[redacted]	[redacted]
Virologic success at week 24 (TLOVR analysis)			
HIV-1 RNA < 50 copies/mL	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Virologic success at week 48 (TLOVR analysis)			
HIV-1 RNA < 50 copies/mL	245 (83.1)	8 (44.4)	253 (80.8)
95% CI	[redacted]	[redacted]	[redacted]
Mean change in Log_{10} VL from baseline (SD)			
Week 24	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]
Mean change in CD4+ count (per µL) from baseline (SD)			
Week 24	145 (131.6)	99 (161.9)	142 (133.6)
Week 48	194 (152.1)	121 (157.0)	190 (153.0)

CI = confidence interval; DRV/COBI = cobicistat-boosted darunavir; NRTI = nucleoside reverse transcriptase inhibitor; RNA = ribonucleic acid; SD = standard deviation; TLOVR = time to loss of virologic response; VL = viral load.
Source: Clinical Study Reports;[7,17] Tashima et al.[8]

3.7 Harms

Only those harms identified in the review protocol (Section 2, Protocol) are reported subsequently (see APPENDIX 4 for detailed harms data.)

The adverse event profile of DRV/COBI 800 mg/150 mg was similar at week 24 and week 48. In addition, the adverse event profile between treatment-naive and treatment-experienced patients was similar; for that reason, data are presented for the total population.

3.7.1 Adverse Events

The primary end point in study GS-US-216-0130 was the incidence of Grade 3 (severe) or Grade 4 (life-threatening) adverse events through week 24. Overall, 16 patients (5.1%) experienced Grade 3 and 2 patients (0.6%) experienced Grade 4 adverse events through week 24 (Table 10). Of the patients who experienced Grade 3 and Grade 4 adverse events, 3 experienced a hypersensitivity reaction and 2 experienced a maculopapular rash.

A total of 91.4% of patients experienced an adverse event of any severity through week 48. The most commonly reported adverse events included diarrhea (27.8%), headache (12.1%), nausea (23.0%), rash (15.7%), and upper respiratory tract infection (14.1%).

3.7.2 Serious Adverse Events

A total of 4.8% and 8.3% of patients experienced a serious adverse event through week 24 and week 48, respectively. There were no particular serious adverse events that occurred more frequently than others.

3.7.3 Withdrawals Due to Adverse Events

A total of 16 (5.1%) treatment-naive patients discontinued study treatment due to an adverse event through week 48. Three patients (1.0%) experienced a rash and another three patients experienced a maculopapular rash that led to discontinuation of the study drug. No treatment-experienced patients discontinued study treatment due to an adverse event.

3.7.4 Mortality

No deaths were reported at week 24 or up to week 48 in study GS-US-216-0130.

3.7.5 Notable Harms

Notable harms identified with input from the consulting clinical expert included metabolic complications, liver complications, renal complications, skin reactions, and cognitive or psychiatric complications. [redacted] experienced an increase in hepatic enzymes though week 48. [redacted] experienced a metabolism or nutrition disorder, with the most common being [redacted] and [redacted]. [redacted] experienced a nervous system disorder, [redacted]. [redacted] experienced abnormal dreams. [redacted] experienced a skin or subcutaneous tissue disorder, [redacted].

[redacted] experienced a renal or urinary disorder through week 24. Renal function was examined more closely due to the inhibitory effects of COBI on tubular secretion of creatinine and subsequent increases in serum creatinine levels. At week 24, there was a mean increase in serum creatinine levels of [redacted] from baseline, and at week 48 there was an increase of 0.10 µmol/L (Table 16). This was accompanied by mean decreases in estimated glomerular filtration rates (SD) of [redacted] at week 24 and [redacted] at week 48.

TABLE 10: HARMS AT WEEK 24 AND WEEK 48

N (%)	Study GS-US-216-0130	
	DRV/COBI 800 mg/150 mg + 2 NRTIs (N = 313)	
	Week 24	Week 48
AEs		
Grade 3 (severe) AEs	16 (5.1)	22 (7.0)
Grade 4 (life-threatening) AEs	2 (0.6)	2 (0.6)
Patients with > 0 AEs	275 (87.9)	286 (91.4)
Most common AEs (≥ 10%)		
Diarrhea	78 (24.9)	[redacted]
Headache	29 (9.3)	38 (12.1)
Nausea	67 (21.4)	72 (23.0)
Rash	[redacted]	[redacted]
Upper respiratory tract infection	31 (9.9)	44 (14.1)

N (%)	Study GS-US-216-0130	
	DRV/COBI 800 mg/150 mg + 2 NRTIs (N = 313)	
	Week 24	Week 48
SAEs		
Patients with > 0 SAEs	15 (4.8)	26 (8.3)
Most common SAEs		
Infections and infestations	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
WDAEs		
AEs leading to study drug discontinuation	15 (4.8)	16 (5.1)
Hypersensitivity	2 (0.6)	2 (0.6)
Nausea	2 (0.6)	2 (0.6)
Rash	3 (1.0)	3 (1.0)
Maculopapular rash	3 (1.0)	3 (1.0)
Deaths		
Number of deaths	0	0
Notable harms		
Hepatobiliary disorders	[redacted]	[redacted]
Hepatic enzyme increased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Anorexia	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]
Hypercholesterolemia	[redacted]	[redacted]
Hypertriglyceridemia	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	29 (9.3)	38 (12.1)
Psychiatric disorders	[redacted]	[redacted]
Abnormal dreams	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]
Pruritis	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]

AE = adverse event; DRV/COBI = cobicistat-boosted darunavir; NRTI = nucleoside reverse transcriptase inhibitor; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Change in the preferred term coding.

Source: Clinical Study Report;[7] Tashima et al.;[8] Summary of Clinical Safety.[9]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was drawn from one phase 3, 48-week, open-label, single-group study. GS-US-216-0130 (N = 314) evaluated the safety and efficacy of DRV/COBI 800 mg/150 mg as separate dosage forms administered in combination with two fully active NRTIs in treatment-naive (n = 296) and treatment-experienced (n = 18) HIV-1–infected patients with no DRV RAMs. Patients who completed 48 weeks of treatment were given the option to continue receiving open-label DRV/COBI 800 mg/150 mg in combination with NRTIs in an open-label rollover phase (no data from this phase were available).

The open-label, single-group design of study GS-US-216-0130 precluded definitive conclusions regarding comparative effectiveness and safety versus other anti-HIV regimens, including DRV/r. With respect to generalizability, the enrolled population reflected a more advanced disease stage than what would be seen in clinical practice, with a lower proportion of Caucasian patients than what would be seen in Canada. As well, almost all of the treatment-naive patients in study GS-US-216-0130 were on a backbone regimen of Truvada ([redacted]), which is a higher proportion than what would be seen in Canadian clinical practice. The treatment-experienced cohort was small (n = 18), limiting the generalizability of these findings to this patient population. There were limited data beyond 48 weeks of treatment and there were no data on quality-of-life outcomes.

The manufacturer submitted two pharmacokinetic bridging studies (TMC114IFD1001 and TMC114IFD1003). These were provided to demonstrate the bioequivalence of DRV boosted with COBI 150 mg versus DRV boosted with RTV 100 mg, and the bioequivalence of DRV 800 mg as an FDC with COBI 150 mg versus DRV 800 mg and COBI 150 mg administered as single drugs (APPENDIX 5: SUMMARY OF DRV/COBI PHARMACOKINETIC STUDIES [TMC114IFD1001 AND TMC114IFD1003]). Health Canada considered that a trial comparing the clinical efficacy and safety of DRV/COBI with DRV/r was not required for approval given the results of the pharmacokinetic bridging studies confirming bioequivalence; the results from the phase 3 trial program for DRV/r; and the safety results for DRV/COBI from study GS-US-216-0130.[14]

4.2 Interpretation of Results

4.2.1 Efficacy

a) Treatment-Naive HIV-1 Patients

The efficacy and safety of DRV/r was assessed in treatment-naive HIV-1 patients in the ARTEMIS[18] study. ARTEMIS (N = 689) was a phase 3 randomized, open-label, 192-week study comparing DRV/r 800 mg/100 mg once daily with ritonavir-boosted lopinavir (LPV/r) 800 mg/200 mg once daily with a backbone regimen of FTC/TDF in treatment-naive HIV-1 patients.[18] ARTEMIS found that DRV/r 800 mg/100 mg was statistically non-inferior and superior to LPV/r 800 mg/200 mg in the proportion of virologic responders (HIV-1 RNA < 50 copies/mL) at week 48 (84% versus 78%) and week 192 (69% versus 57%).

In study GS-US-216-0130, the proportion of treatment-naive patients achieving an HIV-1 RNA VL suppression of below 50 copies/mL with DRV/COBI 800 mg/100 mg was similar at week 24 (83.7%) and week 48 (82.7%). The proportion of treatment-naive HIV-1 patients with virologic failure was also similar at week 24 ([redacted]) and week 48 ([redacted]). As this was a single-group study, it is difficult to estimate the efficacy of DRV/COBI compared with placebo or other anti-HIV regimens with certainty. Naive comparisons with trials of DRV/r are fraught with limitations, as the degree of comparability of trial

populations is uncertain. Nevertheless, the results of study GS-US-216-0130 are generally consistent with those seen at week 48 in the DRV/r group of the ARTEMIS study. In addition, changes from baseline in HIV-1 VL and CD4+ cell count over time in treatment-naive patients from study GS-US-216-0130 (DRV/COBI) and ARTEMIS (DRV/r) followed a similar trend (Figure 2, Figure 3). The clinical expert consulted for this review noted that HIV-1 VL is a more valid measure of clinical efficacy than CD4+ cell counts, which may be more variable.

Without a direct comparative trial, the manufacturer provided an adjusted comparative analysis to compare DRV/COBI 800 mg/150 mg once daily with DRV/r 800 mg/100 mg once daily (see APPENDIX 6). According to this analysis, DRV/COBI was found to be non-inferior to DRV/r based on patients' virologic response at 48 weeks. There was uncertainty with regard to the validity of the results of this analysis. This was due to concerns regarding comparability between treatment groups and the effectiveness of adjustments made for potential confounders; the lack of transparency in the analytical model; and the use of non-standard methods for performing the indirect comparison.

b) Treatment-Experienced HIV-1 Patients

The efficacy and safety of DRV/r was assessed in treatment-experienced HIV-1 patients in the POWER,[19] TITAN,[20] and ODIN[21] studies. POWER 1 and POWER 2 were phase 2, randomized, open-label, 96-week studies. The POWER studies compared DRV/r 600 mg/100 mg twice daily with a control group of investigator-selected PI regimens, plus an optimized background regimen, in highly treatment-experienced HIV-1 patients who had at least one primary PI resistance mutation at screening.[19] Pooled analyses from POWER 1 and POWER 2 (N = 255) showed that the DRV/r 600 mg/100 mg twice-daily group had higher efficacy than the control PI group, based on the proportion of patients with a VL of less than 50 copies/mL at week 48 (45% versus 10%). The DRV/r dose from the POWER studies was used in TITAN (N = 595), a phase 3, randomized, open-label, 96-week study. TITAN compared DRV/r 600 mg/100 mg twice daily with LPV/r 400 mg/100 mg twice daily with an optimized background regimen in treatment-experienced HIV-1 patients.[20] TITAN found that DRV/r 600 mg/100 mg twice daily was non-inferior to LPV/r 400 mg/100 mg twice daily. ODIN (N = 590) was a phase 3, randomized, open-label study. ODIN compared DRV/r 800 mg/100 mg once daily with DRV/r 600 mg/100 mg twice daily with a backbone regimen of two or more investigator-selected NRTIs in treatment-experienced HIV-1 patients who had no DRV RAMs.[21] ODIN found that DRV/r 800 mg/100 mg once daily was non-inferior to DRV/r 600 mg/100 mg twice daily on virologic response at week 48 for HIV-1 patients with no DRV RAMs. Based on the results of the DRV/r clinical trials, the Health Canada–recommended dosing regimen for DRV for treatment-experienced adult patients with at least one DRV RAM is DRV/r 600 mg/100 mg twice daily with food.[5]

In study GS-US-216-0130, the treatment-experienced cohort consisted of 18 patients, limiting the data on the efficacy of DRV/COBI 800 mg/100 mg once daily for this patient population. Consistent with the DRV/r studies, the proportion of virologic responders in treatment-experienced patients was lower than that seen in the treatment-naive cohort (week 24: 61.1%; week 48: 50.0%).

c) Bioequivalence Studies

As described previously, the efficacy of DRV/r in treatment-naive and treatment-experienced patients was established in phase 2 and phase 3 trials. The manufacturer conducted one pharmacokinetic study (TMC114IFD1001) to demonstrate that the bioavailability of DRV 800 mg when boosted with COBI 150 mg was similar to that when boosted with RTV 100 mg (see APPENDIX 5). Study TMC114IFD1001 found that the steady-state DRV C_{max} and AUC_{24h} parameters after repeat dosing confirmed bioequivalence between the COBI and RTV groups, but the DRV C_{min} and C_{0h} parameters were lower in the COBI group compared with the RTV group. The manufacturer noted that the C_{min} and C_{0h} values for DRV 800 mg when boosted

with COBI 150 mg were higher than the half maximal effective concentration (EC_{50}) for both wild-type HIV-1 and DRV-susceptible viruses. However, according to the Health Canada Reviewer's Report, the lower DRV C_{min} and C_{0h} values with COBI were identified as a concern, since treatment-experienced HIV-1 patients with DRV RAMs may have a higher EC_{50}.[14] Should the C_{min} fall lower than the EC_{50} in these patients, there would be a risk of losing virologic suppression. Due to these concerns, the Health Canada–approved indication for DRV/COBI is restricted to patients with no DRV RAMs and, if genetic testing is not feasible, use is recommended in PI-naive patients only. The clinical expert consulted for this review stated that in typical clinical practice, patients with DRV RAMs may be administered DRV/r 600 mg/100 mg twice daily with food to overcome the concern regarding suboptimal trough concentrations.

In study GS-US-216-0130, DRV and COBI were administered as separate drugs instead of an FDC. The manufacturer conducted a single-dose pharmacokinetic study (TMC114IFD1003) that demonstrated the bioequivalence of DRV/COBI 800 mg/150 mg FDC versus the two drugs administered separately (see APPENDIX 5).

d) Adherence

The clinical expert consulted for this review noted that the FDC of DRV/COBI 800 mg/150 mg would be a preferred option to DRV/r 800 mg/100 mg administered as separate drugs due to the potential for better adherence with lower pill burden. Patient group input received by the CADTH Common Drug Review (CDR) on this submission also referenced the potential for improved adherence and convenience of DRV/COBI compared with DRV/r. Poor adherence to treatment regimens plays a significant role in the development of resistance mutations. In study GS-US-216-0130, adherence was generally high, with 95.5% of patients having ≥ 90% adherence by the end of the study. In addition, the development of resistance mutations was low, with only one treatment-experienced patient developing a DRV RAM (that was not associated with phenotypic resistance to DRV), and one treatment-naive patient and one treatment-experienced patient developing an NRTI RAM while receiving FTC. While adherence in clinical practice may be lower than in the controlled setting of a clinical trial, it is reasonable to assume that adherence with the DRV/COBI FDC would be at least as high, and likely higher, than DRV and RTV or COBI administered separately.

4.2.2 Harms

The incidence of adverse events in study GS-US-216-0130 was similar through week 24 and week 48. The most common adverse events were diarrhea, headache, nausea, rash, and upper respiratory tract infections. A total of 16 treatment-naive patients (5.1%) withdrew from study treatment due to an adverse event, with 6 patients withdrawing due to rash. There were no deaths reported until week 48.

[redacted] treatment-experienced patients were on a backbone regimen of AZT plus FTC/TDF, which is not normally used in current Canadian clinical practice due to adverse effects, according to the clinical expert consulted for this review. This may have impacted the adverse event profile in the study, but the impact would be minimal as few patients were on this background regimen. Generally, the incidence of adverse events did not differ greatly between treatment-naive and treatment-experienced patients.

Skin reactions were observed during the clinical development program for DRV.[5] In study GS-US-216-0130, skin and subcutaneous tissue disorders were reported in [redacted] patients. The clinical expert consulted for this review indicated that skin reactions with DRV are usually not a major concern and rarely lead to treatment discontinuation. The Health Canada product monograph for DRV/COBI contains a warning to discontinue treatment immediately if signs or symptoms of severe skin reactions develop.[22]

COBI has been known to inhibit creatinine tubular secretion and thereby increase serum creatinine levels.[6] In study GS-US-216-0130, there was a decrease from baseline in estimated glomerular filtration rate at week 24 and week 48, with a concomitant increase from baseline in serum creatinine levels at week 24 and week 48. [redacted] patients experienced a renal or urinary disorder. The clinical expert consulted for this review did not expect these changes to cause concern, although patients would be monitored for renal function regularly. A phase 3 study is currently being conducted (projected completion February 2015) that assesses the safety and tolerability of COBI-containing regimens in HIV-1 patients with mild to moderate renal impairment (clinicaltrials.gov NCT01363011).[23]

While informal indirect comparisons are prone to bias, overall, the adverse event profile of DRV/COBI appears to be similar to DRV/r.[5] Unfortunately, the manufacturer's adjusted analysis of DRV/COBI compared with DRV/r did not assess safety outcomes. In the patient group input received by CDR on this submission, concerns were expressed regarding fatigue, high cholesterol, and gastrointestinal adverse effects. While DRV was generally considered to be well tolerated, ritonavir was perceived to be associated with considerable gastrointestinal effects. Diarrhea and nausea occurred in a considerable proportion (more than 20%) of patients in the GS-US-216-0130 study. Reported rates of diarrhea with DRV/r were 8% to 14% for diarrhea and 4% to 7% for nausea.[24] While direct comparison of these figures with the DRV/COBI data is difficult, they do not suggest that DRV/COBI has better gastrointestinal tolerability than DRV/r.

As COBI is a selective inhibitor of CYP3A, it is expected to result in fewer and more predictable off-target drug interactions.[6] RTV does not selectively inhibit CYP3A and may induce the activity of CYP1A2, CYP2C0 and CYP2C19, resulting in more off-target drug interactions.[6]

4.3 Other Considerations

DRV/r is indicated for treatment-experienced pediatric patients from 3 to 18 years of age using a weight-based dosing (in tablet form or with an oral suspension) that does not exceed 600 mg/100 mg twice daily.[5] DRV/COBI has not been studied in a pediatric population, but a phase 2/3 trial is currently under way to study the pharmacokinetics, safety, and efficacy of DRV/COBI and atazanavir/COBI in treatment-experienced HIV-1 patients between 3 and 18 years of age (clinicaltrials.gov NCT02016924).[25]

5. CONCLUSIONS

In one phase 3, open-label, single-group study, DRV/COBI 800 mg/150 mg administered as single drugs was shown to achieve relatively high rates of VL suppression (HIV-1 RNA < 50 copies/mL) in treatment-naive and treatment-experienced adult patients with HIV-1 infection, although data for the treatment-experienced population were limited, as only 18 such patients were enrolled in the trial. Efficacy results for both populations were broadly similar to those for DRV/r in previous studies, although definitive conclusions regarding comparative efficacy and safety could not be drawn without a direct comparative trial. There were no data available on quality-of-life outcomes. The most commonly reported adverse events included diarrhea, headache, nausea, and rash. Rash was the most common adverse event that led to treatment discontinuation in treatment-naive patients. Although serum creatinine levels increased from baseline, there were few renal-related adverse events.

Pharmacokinetic data demonstrated bioequivalence of DRV/COBI 800 mg/150 mg versus DRV/r 800 mg/100 mg with respect to DRV maximum plasma concentrations and AUC_{24h} values, but DRV C_{min} and C_{0h} parameters were lower with COBI than with RTV. Bioequivalence was also demonstrated for DRV/COBI 800 mg/150 mg FDC versus administration as single drugs.

APPENDIX 1: PATIENT INPUT SUMMARY

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

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

The Canadian Treatment Action Council (CTAC) is a national non-governmental organization addressing access to treatment, care, and support for people living with HIV and hepatitis C. CTAC's organizational goals are to meaningfully engage community members, service providers, policy-makers, and other relevant stakeholders to identify, develop, and implement policy and program solutions.

CTAC received unrestricted organizational and educational grants from the following organizations in the 2013–2014 fiscal year: Abbott/Abbvie, Boehringer Ingelheim, Gilead Sciences, Janssen, and ViiV Healthcare. CTAC declared no conflict of interest in the preparation of its submission.

2. Condition and Current Therapy-Related Information

Information for this submission was collected from a survey (five HIV-positive individuals responded) in follow-up to a national webinar on the CADTH Common Drug Review (CDR) patient input process and key findings from the Prezcobix clinical trials, and survey data used in submissions for Stribild, Tivicay, and Triumeq.

HIV is a serious, life-threatening illness that threatens the immune system. Over time, if left untreated, HIV can compromise a person's immune system to the point that the body may no longer be able to fight off opportunistic infections. At that point, an AIDS diagnosis as well as death may occur. In most cases, people taking highly active antiretroviral treatment achieve an undetectable viral load (or viral suppression) and can live long lives, managing their HIV as a chronic illness.

HIV can present a number of complications, and these can vary day to day and from patient to patient. Many people living with HIV experience negative mental health outcomes, either as side effects from treatment, or from facing stigma and discrimination and related stress. Most of these individuals also experience fatigue, both before and after they initiate treatment, making it difficult to maintain diet and exercise routines, and even to work. A few respondents stated that their quality of life related to these areas has improved as a result of treatment. A few respondents as well as caregivers noted the substantial impact that the social determinants of health, particularly living conditions, have had on managing their HIV. One patient noted: *"… Taking the medication, side effects and having poverty, no food and no housing. Navigating through social services, addictions and child protection safely. How does a parent take medications consistently when they are worried about their children being apprehended.[sic]"*

All five survey respondents are currently on HIV therapy. Four have been on a treatment regimen ranging from one to 30 years and on their current treatment regimen from one to six years (median = 4). The four respondents noted that their current HIV therapy includes darunavir/ritonavir plus tenofovir plus lamivudine; Complera; Isentress; and Intelence plus Kivexa. They expressed concern about adverse events including fatigue, high cholesterol, loose stools, and "big stomach."

Patients who responded to the Stribild, Tivicay, and Triumeq surveys also indicated several advantages and challenges with current therapy. While these respondents indicated that the adverse events with darunavir have been minor, one of the respondents reported several gastrointestinal adverse events

due to ritonavir, specifically *"… GI distress, diarrhea, gas, weight gain.*" This adverse event is particularly important to include in this submission as ritonavir has typically been used as a booster with darunavir, and Prezcobix now offers cobicistat as an alternative pharmacoenhancer in a fixed-dose combination regimen.

Respondents identified lack of funding and transportation costs as barriers to accessing treatment. Respondents from previous patient input surveys highlighted that the challenges — including 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. Patients also noted difficulties when being obliged to seek services from specialists.

3. Related Information About the Drug Being Reviewed

None of the five survey respondents had experience with the treatment under consideration. Out of five respondents, one person stated he was not certain if he would consider taking Prezcobix instead of current therapy or therapy taken in the past. He was not certain if the side effects associated with Prezcobix seemed more severe, less severe, or similar to current or past therapy. Another respondent suggested that the adverse events would be similar to currently existing treatment and noted that adverse events would more likely be associated with the product if a Kivexa backbone regimen were administered. During the webinar discussions, a participant expressed the need for more information about the safety profile of cobicistat compared with ritonavir. While noting the benefit of Prezcobix is its simplified dosing, which may increase adherence and convenience, the participant stated that cobicistat does not appear to be an improvement over ritonavir in terms of gastrointestinal adverse events.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search:	October 28, 2014
Alerts:	Bi-weekly search updates until March 18, 2015
Study types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

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

MULTI-DATABASE STRATEGY	
1	prezcobix.ti,ab.
2	(Darunavir* or Darunavirum or DRV or HSDB 7788 or Prezista or TMC 114 or TMC 41629 or TMC114 or TMC41629).ti,ab.
3	*darunavir/
4	or/2-3
5	(Cobicistat* or Tybost or COBI or GS 9350 or GS9350).ti,ab.
6	*cobicistat/

MULTI-DATABASE STRATEGY	
7	or/5-6
8	and/4,7
9	or/1,8
10	conference abstract.pt.
11	9 not 10
12	11 use oemezd
13	Prezcobix.ti,ab,rn,nm,sh,hw,ot.
14	(Darunavir* or Darunavirum or DRV or HSDB 7788 or HSDB7788 or Prezista or TMC 114 or TMC 41629 or TMC114 or TMC41629).ti,ab,rn,nm,sh,hw,ot.
15	(UIC 94017 or UIC94017 or YO603Y8113 or 206361-99-1 or 1097732-88-1 or 618109-00-5).rn,nm.
16	or/14-15
17	(Cobicistat* or Tybost or COBI or GS 9350 or GS9350).ti,ab,rn,nm,sh,hw,ot.
18	(1004316-88-4 or LW2E03M5PG).rn,nm.
19	or/17-18
20	and/16,19
21	or/13,20
22	21 use pmez
23	or/12,22
24	remove duplicates from 23

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	October 15-23, 2014
Keywords:	Prezcobix (darunavir and cobicistat), HIV
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Kakuda et al. (2014)[26]	Study design
Kakuda et al. (2014)[27]	

APPENDIX 4: DETAILED OUTCOME DATA

Virologic Outcomes

TABLE 11: VIROLOGIC OUTCOME AT WEEK 24 AND WEEK 48 (SNAPSHOT ANALYSIS)

	Study GS-US-216-0130		
	DRV/COBI 800 mg/150 mg + 2 NRTIs		
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Virologic success at week 24			
HIV-1 RNA < 50 copies/mL	247 (83.7)	11 (61.1)	258 (82.4)
95% CI, %	79.0, 87.8	[redacted]	77.8, 86.5
Virologic success at week 48			
HIV-1 RNA < 50 copies/mL	244 (82.7)	9 (50.0)	253 (80.8)
95% CI, %	77.9, 86.8	[redacted]	76.0, 85.0
Virologic failure at week 24			
Virologic failure	[redacted]	[redacted]	36 (11.5)
HIV-1 RNA ≥ 50 copies/mL	[redacted]	[redacted]	22 (7.0)
Discontinued study drug due to lack of efficacy	[redacted]	[redacted]	0
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥ 50 copies/mL	[redacted]	[redacted]	14 (4.5)
No virologic data in window	[redacted]	[redacted]	19 (6.1)
Discontinued study drug due to AE/death	[redacted]	[redacted]	14 (4.5)
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL	[redacted]	[redacted]	3 (1.0)
Missing data during window but on study drug	[redacted]	[redacted]	2 (0.6)
Virologic failure at week 48			
Virologic failure	[redacted]	[redacted]	33 (10.5)
HIV-1 RNA ≥ 50 copies/mL	[redacted]	[redacted]	14 (4.5)
Discontinued study drug due to lack of efficacy	[redacted]	[redacted]	0
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥ 50 copies/mL	[redacted]	[redacted]	19 (6.1)
No virologic data in window	[redacted]	[redacted]	27 (8.6)
Discontinued study drug due to AE/death	[redacted]	[redacted]	15 (4.8)
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL	[redacted]	[redacted]	10 (3.2)
Missing data during window but on study drug	[redacted]	[redacted]	2 (0.6)

AE = adverse event; CI = confidence interval; DRV/COBI = cobicistat-boosted darunavir; NRTI = nucleoside reverse transcriptase inhibitor; RNA = ribonucleic acid.
Source: Clinical Study Reports;[7,17] Tashima et al.[8]

TABLE 12: VIROLOGIC OUTCOME AT WEEK 24 AND WEEK 48 (TLOVR ANALYSIS)

	Study GS-US-216-0130 DRV/COBI 800 mg/150 mg + 2 NRTIs		
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Virologic success at week 24			
HIV-1 RNA < 50 copies/mL	[redacted]	[redacted]	[redacted]
95% CI, %	[redacted]	[redacted]	[redacted]
Virologic success at week 48			
HIV-1 RNA < 50 copies/mL	245 (83.1)	8 (44.4)	253 (80.8)
95% CI, %	[redacted]	[redacted]	[redacted]
Loss of virologic response through week 24			
Virologic failure	[redacted]	[redacted]	[redacted]
Rebound	[redacted]	[redacted]	[redacted]
Never suppressed through time of analysis	[redacted]	[redacted]	[redacted]
Drug discontinuation due to lack of efficacy	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Drug discontinuation due to AEs	[redacted]	[redacted]	[redacted]
Drug discontinuation due to other reasons	[redacted]	[redacted]	[redacted]
Loss of virologic response through week 48			
Virologic failure	[redacted]	[redacted]	[redacted]
Rebound	[redacted]	[redacted]	[redacted]
Never suppressed through time of analysis	[redacted]	[redacted]	[redacted]
Drug discontinuation due to lack of efficacy	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Drug discontinuation due to AEs	[redacted]	[redacted]	[redacted]
Drug discontinuation due to other reasons	[redacted]	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; DRV/COBI = cobicistat-boosted darunavir; NRTI = nucleoside reverse transcriptase inhibitor; RNA = ribonucleic acid; TLOVR = time to loss of virologic response.
Source: Clinical Study Reports;[7,17] Tashima et al.[8]

TABLE 13: CHANGE FROM BASELINE IN PLASMA HIV-1 RNA

Log_{10} HIV-1 RNA	Study GS-US-216-0130 DRV/COBI 800 mg/150 mg + 2 NRTIs		
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Baseline			
N	295	18	313
Mean (SD)	4.75 (0.76)	4.83 (1.04)	4.76 (0.78)
Week 24			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]
Week 48			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]

DRV/COBI = cobicistat-boosted darunavir; NRTI = nucleoside reverse transcriptase inhibitor; SD = standard deviation.
Source: Clinical Study Reports.[7,17]

CD4+ Cell Counts

TABLE 14: CHANGE FROM BASELINE IN CD4+ CELL COUNT

CD4+ Count, /µL	Study GS-US-216-0130		
	DRV/COBI 800 mg/150 mg + 2 NRTIs		
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Baseline			
N	295	18	313
Mean (SD)	378 (199.9)	198 (214.3)	368 (204.8)
Week 24			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	145 (131.6)	99 (161.9)	[redacted]
Week 48			
N	261	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	194 (152.1)	121 (157.0)	[redacted]

DRV/COBI = cobicistat-boosted darunavir; NRTI = nucleoside reverse transcriptase inhibitor; SD = standard deviation.
Source: Clinical Study Reports.[7,17]

Resistance Mutations

TABLE 15: DEVELOPMENT OF HIV-1 GENOTYPIC RESISTANCE AT WEEK 24 AND WEEK 48

Resistance Development Category	Study GS-US-216-0130	
	DRV/COBI 800 mg/150 mg + 2 NRTIs	
	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)
Week 24		
Virologic failure at week 24 (Snapshot analysis)	[redacted]	[redacted]
Virologic failure at week 24 (TLOVR analysis)	[redacted]	[redacted]
Resistance analysis population	[redacted]	[redacted]
Developed resistance mutations to darunavir	[redacted]	[redacted]
Developed resistance mutations to NRTI regimen	[redacted]	[redacted]
Week 48		
Virologic failure at week 48 (Snapshot analysis)	24 (8.1)	9 (50.0)
Virologic failure at week 48 (TLOVR analysis)	[redacted]	[redacted]
Resistance analysis population	[redacted]	[redacted]
Developed resistance mutations to darunavir	[redacted]	[redacted]
Developed resistance mutations to NRTI regimen	[redacted]	[redacted]

DRV/COBI = cobicistat-boosted darunavir; NRTI = nucleoside reverse transcriptase inhibitor; TLOVR = time to loss of virologic response.
[a] The resistance analysis population included patients who were on study drugs and experienced either suboptimal virologic response (HIV-1 RNA ≥ 50 copies/mL **and** < 1 $\log_{10}$ reduction from baseline at week 8 and confirmed at week 12), or virologic rebound (two subsequent visits with HIV-1 RNA ≥ 400 copies/mL after achieving HIV-1 RNA < 50 copies/mL, or as having two subsequent visits with > 1 $\log_{10}$ increase in HIV-1 RNA from their nadir), either of which was considered virologic failure.
Source: Clinical Study Reports;[7,17] Tashima et al.[8]

Safety — Renal Parameters

TABLE 16: RENAL PARAMETERS AT WEEK 24 AND WEEK 48

Mean (SD) Change From Baseline	Study GS-US-216-0130	
	DRV/COBI 800 mg/150 mg + 2 NRTIs (N = 313)	
	Week 24	Week 48
Serum creatinine, µmol/L	[redacted]	0.10 (NR)
eGFR, mL/min	[redacted]	[redacted]

DRV/COBI = cobicistat-boosted darunavir; eGFR = estimated glomerular filtration rate; NRTI = nucleoside reverse transcriptase inhibitor; SD = standard deviation.
Source: Summary of Clinical Safety.[9]

APPENDIX 5: SUMMARY OF DRV/COBI PHARMACOKINETIC STUDIES (TMC114IFD1001 AND TMC114IFD1003)

Objective

To summarize the pharmacokinetic findings of two phase 1, open-label, randomized, crossover bioequivalence studies relevant to cobicistat-boosted darunavir (DRV/COBI). One study (TMC114IFD1001)[27,28] compared DRV/COBI with ritonavir-boosted darunavir (DRV/r), and the other (TMC114IFD1003)[26,29] compared DRV/COBI administered as a fixed-dose combination (FDC) versus darunavir (DRV) plus cobicistat (COBI) administered as single drugs.

Study Characteristics

Study TMC114IFD1001 (N = 36) was a randomized, three-way crossover study in which all patients received each treatment regimen for a duration of 10 days, with a washout period of at least 7 days between treatments. This study consisted of three treatment regimens: DRV 800 mg and ritonavir (RTV) 100 mg given once daily as separate drugs, and DRV/COBI 800 mg/150 mg as an FDC in two different formulations (G003 and G004). Study TMC114IFD1003 (N = 133) was a randomized, crossover study in which patients were randomized to one of three panels in which they would receive a single dose each of two treatments: DRV/COBI as single drugs or as an FDC under fasted or fed conditions, with a washout period of at least 7 days between each treatment. Both studies were conducted in healthy, HIV-negative volunteers (Table 17).

TABLE 17: SUMMARY OF TMC114IFD1001 AND TMC114IFD1003

	TMC114IFD1001[27,28]	TMC114IFD1003[26,29]
Design	OL, randomized, three-way crossover study (six-sequence three-period Williams design)	OL, randomized, three-panel crossover study
Population	Healthy, HIV-negative adults	
N	36 randomized and treated	133 randomized and treated
Treatments	• A: DRV 800 mg QD + RTV 100 mg QD • B: DRV/COBI 800 mg/150 mg FDC QD (G003) • C: DRV/COBI 800 mg/150 mg FDC QD (G004) Each treatment was administered at the same time each day with a standardized breakfast (21 g fat, 533 kCal)	**Panel 1 (n = 74)** • A: DRV 800 mg QD+COBI 150 mg QD separate drugs, fasted • B: DRV/COBI 800 mg/150 mg FDC QD, fasted **Panel 2 (n = 40)** • C: DRV 800 mg QD+COBI 150 mg QD separate drugs, standardized breakfast • D: DRV/COBI 800 mg/150 mg FDC QD, standardized breakfast **Panel 3 (n = 19)** • E: DRV/COBI 800 mg/150 mg FDC QD, fasted • F: DRV/COBI 800 mg/150 mg FDC QD, standardized high-fat breakfast
Duration of each treatment period	10 days	Single dose

	TMC114IFD1001[27,28]	TMC114IFD1003[26,29]
Duration of washout period	≥ 7 days	
Female, N (%)	30 (83.3)	59 (44.4)
Median age, years (range)	46.5 (20, 55)	46.0 (19, 60)
Median BMI, kg/m^2 (range)	24.3 (20.6, 29.5)	25.2 (19, 30)
Outcomes	**Pharmacokinetic parameters (taken after dosing on day 10)** • C_{0h}: pre-dose (trough) plasma concentration • C_{24h}: plasma concentration at 24 hours • C_{max}: maximum plasma concentration • C_{min}: minimum plasma concentration • AUC_{24h}: area under the plasma concentration-time curve from time of administration to 24 hours after dosing Bioequivalence established if 90% CI of the LS means ratio for the test versus reference were within the limits of 80% to 125%	**Pharmacokinetic parameters** • C_{max}: maximum plasma concentration • C_{last}: last observed measurable (not below quantification limit) analyte concentration • t_{max}: actual sampling time to reach the maximum plasma analyte concentration • AUC_{last}: AUC from time of administration up to the last time point with a measurable plasma concentration post dosing • AUC_{∞}: AUC extrapolated to infinity, calculated as $AUC_{last} + C_{last}/\lambda_z$ • Λ_z: terminal elimination rate constant • $t_{1/2term}$: terminal elimination half-life, defined as $0.693/\lambda_z$

AUC = area under the curve; BMI = body mass index; CI = confidence interval; COBI = cobicistat; DRV = darunavir; DRV/COBI = cobicistat-boosted darunavir; FDC = fixed-dose combination; LS = least squares; OL = open-label; QD = once daily; RTV = ritonavir.
Source: Clinical Study Reports;[28,29] Kakuda et al. (2014);[27] Kakuda et al. (2014).[26]

In study TMC114IFD1001, six volunteers discontinued treatment prior to the end of the study (Figure 4). Five volunteers discontinued due to an adverse event and one withdrew consent. Two volunteers discontinued treatment due to an adverse event (rash) during intake of DRV/r; the rest discontinued during intake of DRV/COBI (rash and maculopapular rash). In study TMC114IFD1003, three volunteers discontinued from the study: one for a protocol violation (Panel 1) and two withdrew consent (Panel 2) (Figure 5).

FIGURE 4: PATIENT DISPOSITION IN STUDY TMC114IFD1001

Confidential figure removed at manufacturer's request
Source: Clinical Study Report.[28]

FIGURE 5: PATIENT DISPOSITION IN STUDY TMC114IFD1003

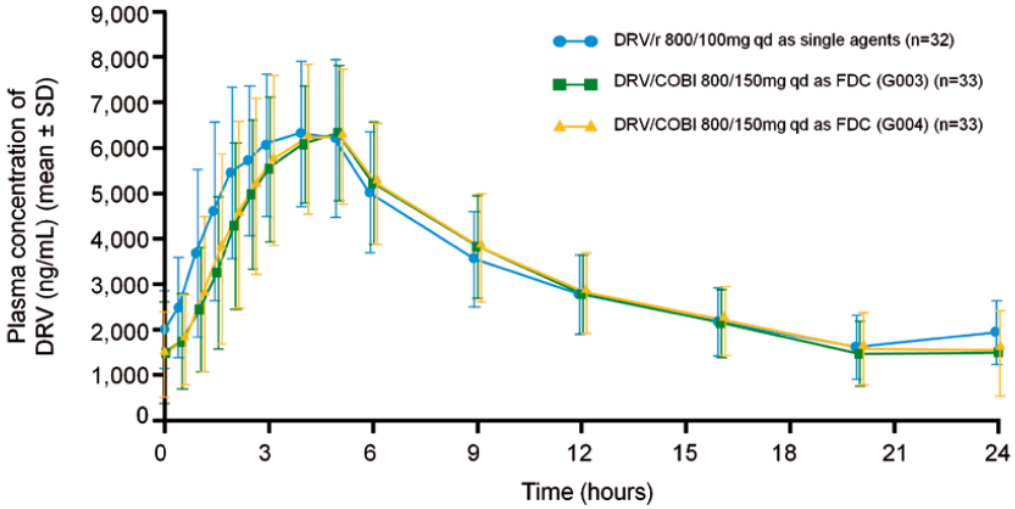
Confidential figure removed at manufacturer's request
Source: Clinical Study Report.[29]

Results

Study TMC114IFD1001

The mean plasma concentration-time curves of DRV were similar among the three treatment regimens (Figure 6). The DRV pharmacokinetic parameters C_{max} and AUC_{24h} were similar after 10 days of dosing with DRV 800 mg under fed conditions, whether boosted with RTV 100 mg once daily or COBI 150 mg once daily (Table 18). Both the C_{max} and AUC_{24h} parameters fell within the limits of bioequivalence for DRV/r as well as both the G003 and G004 formulations of DRV/COBI FDC, as the 90% confidence intervals of the least squares–mean ratios were between 80% and 125%. However, the DRV pharmacokinetic parameters C_{0h} and C_{min} were lower in the DRV/COBI regimens compared with the DRV/r regimen, and the 90% confidence intervals of the least squares–mean ratios fell outside the 80% to 125% range.

FIGURE 6: DRV PLASMA CONCENTRATION-TIME PROFILES OF DRV 800 MG WITH COBI 150 MG VERSUS DRV 800 MG WITH RTV 100 MG AT DAY 10 (STUDY TMC114IFD1001)



COBI = cobicistat; DRV = darunavir; DRV/COBI = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; FDC = fixed-dose combination; QD = once daily; RTV = ritonavir; SD = standard deviation.
Source: Kakuda et al. (2012) poster.[30]

TABLE 18: PHARMACOKINETIC PARAMETERS OF DARUNAVIR IN STUDY TMC114IFD1001, FED CONDITIONS

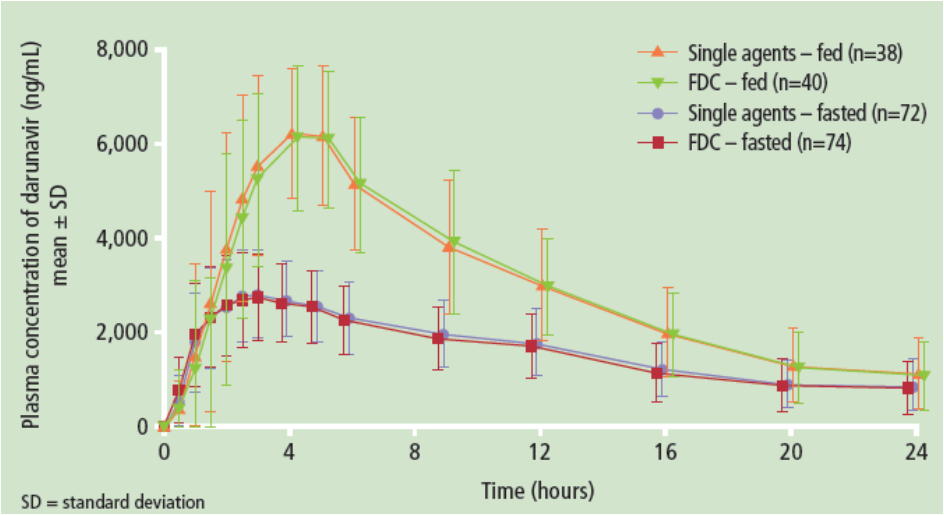
Parameter, Mean ± SD	DRV/r 800 mg/100 mg QD (Reference) (N = 32)	DRV/COBI 800 mg/150 mg FDC QD (G003) (N = 33)	LSM Ratio (90% CI)	DRV/COBI 800 mg/150 mg FDC QD (G004) (N = 33)	LSM Ratio (90% CI)
C_{0h}, ng/L	2,015 ± 852.3	1,504 ± 1114	0.65 (0.55, 0.76)	1,478 ± 933.8	0.68 (0.57, 0.80)
C_{24h}, mg/L	1,958 ± 708.2	1,506 ± 935.8	ND	1,566 ± 885.1	ND
C_{min}, ng/L	1,540 ± 610.7	1,167 ± 786.6	0.69 (0.60 to 0.81)	1,224 ± 680.6	0.74 (0.63 to 0.86)
C_{max}, ng/mL	6,973 ± 1,527	6,666 ± 1287	**0.97 (0.92 to 1.01)**	6,917 ± 1,394	**1.00 (0.96 to 1.04)**
AUC_{24h}, ng·h/mL	78,410 ± 20,910	74,780 ± 19,750	**0.97 (0.92 to 1.02)**	76,490 ± 20,900	**0.99 (0.94 to 1.04)**

AUC = area under the curve; CI = confidence interval; DRV/COBI = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; FDC = fixed-dose combination; LSM = least squares mean; ND = not determined; QD = once daily; SD = standard deviation.
Data in bold face indicate parameters that met the criteria for statistical significance.
Source: Clinical Study Report;[28] Kakuda et al. (2014).[27]

Study TMC114IFD1003

The mean plasma concentration-time curves of DRV administered with COBI were similar between the FDC and single drugs, under fed or fasted conditions (Figure 7). Bioequivalence was demonstrated between the DRV/COBI 800 mg/150 mg FDC and the single drugs, under both fasted (Table 19) and fed (Table 20) conditions, as the 90% confidence intervals of the least squares–mean ratios for C_{max}, AUC_{last}, and AUC_{∞} of darunavir all fell between 80% and 125%.

FIGURE 7: DARUNAVIR PLASMA CONCENTRATION-TIME PROFILES OF A SINGLE DOSE OF DRV 800 MG WITH COBI 150 MG AS EITHER FDC OR SINGLE DRUGS, UNDER FASTED (PANEL 1) OR FED (PANEL 2) CONDITIONS (STUDY TMC114IFD1003)



COBI = cobicistat; DRV = darunavir; FDC = fixed-dose combination; SD = standard deviation.
Source: Kakuda et al. (2013) poster.[31]

TABLE 19: PHARMACOKINETIC PARAMETERS OF DARUNAVIR IN STUDY TMC114IFD1003, FASTED CONDITIONS

Parameter Mean ± SD; t_{max} and t_{last}: Median (Range)	DRV/COBI 800 mg/150 mg as Single Drugs (N = 72)	DRV/COBI 800 mg/150 mg FDC (G006) (N = 74)	LSM Ratio (90% CI)
C_{max}, ng/mL	3,129 ± 933	3087 ± 927	**98.59 (93.72 to 103.73)**
t_{max}, h	3.00 (1.00 to 12.00)	3.00 (1.00 to 12.00)	–
AUC_{last}, ng·h/mL	47,326 ± 18,314	46,329 ± 18,476	**96.20 (90.98 to 101.71)**
AUC_{∞}, ng·h/mL	47,668 ± 18,689	46,291 ± 18,781	**96.00 (90.30 to 102.07)**
$t_{1/2term}$, h	7.2 ± 3.3	7.6 ± 3.5	–

AUC = area under the curve; CI = confidence interval; DRV/COBI = cobicistat-boosted darunavir; FDC = fixed-dose combination; LSM = least squares mean; SD = standard deviation.
Data in bold face indicate parameters that met the criteria for statistical significance.
Source: Clinical Study Report;[29] Kakuda et al. (2014).[26]

TABLE 20: PHARMACOKINETIC PARAMETERS OF DARUNAVIR IN STUDY TMC114IFD1003, FED CONDITIONS

Parameter Mean ± SD; t_{max} and t_{last}: Median (Range)	DRV/COBI 800 mg/150 mg as Single Drugs (N = 38)	DRV/COBI 800 mg/150 mg FDC (G006) (N = 40)	LSM Ratio (90% CI)
C_{max}, ng/mL	6,979 ± 1,201	6,773 ± 1,343	**96.79 (93.06 to 100.60)**
t_{max}, h	4.00 (1.00 to 9.00)	4.03 (1.50 to 9.05)	–
AUC_{last}, ng·h/mL	81,483 ± 27,540	78,942 ± 26,709	**97.71 (93.08 to 102.57)**
AUC_{∞}, ng·h/mL	79,836 ± 26,913	78,811 ± 27,304	**97.81 (92.85 to 13.05)**
$t_{1/2term}$, h	5.5 ± 1.6	6.7 ± 3.4	–

AUC = area under the curve; CI = confidence interval; DRV/COBI = cobicistat-boosted darunavir; FDC = fixed-dose combination; LSM = least squares mean; SD = standard deviation.
Note: Data in bold indicate parameters that met the criteria for statistical significance.
Source: Clinical Study Report;[29] Kakuda et al. (2014).[26]

Conclusions

Study TMC114IFD1001 demonstrated that the DRV/COBI 800 mg/150 mg FDC tablet provided DRV exposures that were comparable to those obtained with DRV boosted with RTV 100 mg once daily. The DRV C_{max} and AUC_{24h} parameters were bioequivalent between the COBI and RTV groups; however, the C_{min} and C_{0h} were lower in the COBI group compared with the RTV group. Study TMC114IFD1003 demonstrated that DRV/COBI 800 mg/150 mg FDC was bioequivalent to co-administration as single drugs.

APPENDIX 6: SUMMARY AND CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED COMPARATIVE ANALYSIS

Objective

To summarize and appraise the methods and results of a manufacturer-submitted comparative analysis of cobicistat-boosted darunavir (DRV/COBI) versus ritonavir-boosted darunavir (DRV/r).

Study Characteristics/Methods

The primary objective of this study was to demonstrate non-inferiority in overall response (patients achieving an HIV-1 RNA of less than 50 copies/mL) with DRV/COBI versus DRV/r, within a margin of 12%. Patient-level data were obtained from three phase 3 trials: study SG 216 0130 for DRV/COBI (reviewed in detail in the main body of this report), and the ARTEMIS (TMC-114-C211) and ODIN (TMC114-C229) studies for DRV/r. ARTEMIS was a randomized, comparative, phase 3, non-inferiority trial of treatment-naive patients treated with DRV/r or ritonavir-boosted lopinavir (LPV/r). The study had a 192-week treatment period where patients received DRV/r 800 mg/100 mg once daily (n = 343) or LPV/r 800 mg/200 mg once daily (n = 346) in combination with a background regimen of emtricitabine/tenofovir (FTC/TDF). The ODIN study was a randomized, open-label, comparative, phase 3, non-inferiority trial of treatment-experienced patients with no darunavir resistance-associated mutations. Patients were treated with DRV/r 800 mg/100 mg (n = 294) once daily or 600 mg/100 mg twice daily (n = 296) as single drugs in combination with an investigator-selected optimized background therapy of ≥ 2 nucleoside reverse transcriptase inhibitors.

For the purposes of the comparative analysis, the DRV/r 800 mg/100 mg groups from both ARTEMIS and ODIN were utilized as a comparator with the GS-US-216-0130 DRV/COBI group. The primary outcome was virological response at 48 weeks, which was defined as the proportion of patients with an HIV-1 RNA of less than 50 copies/mL (Snapshot algorithm). The results of the virologic response (based on time to loss of virologic response) were presented as a sensitivity analysis. The statistical analysis was performed on the overall dataset of the GS-US-216-0130 study's DRV/COBI 800 mg/150 mg once-daily group versus the pooled DRV/r 800 mg/100 mg once-daily groups of the ARTEMIS and ODIN trials, using a multivariate logistic regression model. Indicators for treatment, age, gender, race, baseline CD4, baseline HIV RNA, HIV disease status, level of adherence, and previous antiretroviral therapy use were included as covariates in the model (Table 21). To improve model fit, a variable selection procedure was applied. Both the backward selection and the stepwise selection procedures were considered, at a significance level of 10%. Treatment effect was retained in the model regardless whether the effect was statistically significant at this level. The final result was presented as an odds ratio (OR) comparing the two treatment regimens based on the reduced model. To convert the OR to a risk difference for assessment of non-inferiority (based on the margin of 12% on the risk difference), an assumed event rate of 80% was used in GS-US-216-0130. Accordingly, the non-inferiority margin on the OR scale was 0.531.

TABLE 21: BASELINE CHARACTERISTICS IN THE GS-US-216-0130, ARTEMIS, AND ODIN STUDIES

Variable	Categories	DRV/COBI		DRV/r	
		GS-US-216-0130 (N = 313)	ARTEMIS (N = 343)	ODIN (N = 294)	Pooled (N = 637)
Age (years)	≤ 30	98 (31%)	99 (29%)	31 (11%)	130 (20%)
	30 to ≤ 45	134 (43%)	187 (55%)	176 (60%)	363 (57%)
	45 to ≤ 55	63 (20%)	45 (13%)	65 (22%)	110 (17%)
	55+	18 (6%)	12 (3%)	22 (7%)	34 (5%)
Race	Caucasian	130 (42%)	137 (40%)	102 (35%)	239 (38%)
	Black	106 (34%)	80 (23%)	83 (28%)	163 (26%)
	Asian/Oriental	4 (1%)	44 (13%)	48 (16%)	92 (14%)
	Hispanic	68 (22%)	77 (22%)	47 (16%)	124 (19%)
	Other	5 (2%)	5 (1%)	14 (5%)	19 (3%)
Gender	Male	279 (89%)	239 (70%)	179 (61%)	418 (66%)
Baseline viral load	≤ 100,000	201 (64%)	226 (66%)	255 (87%)	481 (76%)
	> 100,000	112 (36%)	117 (34%)	39 (13%)	156 (24%)
Baseline CD4+ count (× 10^6 cell/L)	≤ 200	59 (19%)	141 (41%)	125 (43%)	266 (42%)
	200 to 350	87 (28%)	130 (38%)	108 (37%)	238 (37%)
	≥ 350	167 (53%)	72 (21%)	61 (21%)	133 (21%)
HIV disease status[a]	A	251 (80%)	226 (66%)	107 (36%)	333 (52%)
	B	28 (9%)	91 (27%)	79 (27%)	170 (27%)
	C	34 (11%)	26 (8%)	108 (37%)	134 (21%)
Level of adherence[b]	> 95%	283 (90%)	329 (96%)	189 (64%)	518 (81%)
	≤ 95%	30 (10%)	14 (4%)	105 (36%)	119 (19%)
Previous ARV used	None	296 (95%)	343 (100%)	2 (1%)	345 (54%)
	NRTIs + NNRTIs or NRTIs only	8 (2%)	0	185 (63%)	185 (29%)
	Any combination with PIs	9 (3%)	0	107 (36%)	107 (17%)

ARV = antiretroviral; DRV/COBI = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

[a] World Health Organization (WHO) stages are mapped to Centers for Disease Control and Prevention (CDC) stages as follows: WHO stage 1 = CDC category A; WHO stage 2 = CDC category B; WHO stage 3 = CDC category C (if CD4 is less than 200 cells/µL and B otherwise); WHO stage 4 = CDC category C.

[b] Darunavir adherence was computed as the number of pills actually taken divided by the number of pills expected to be taken (in per cent): the number of pills actually taken was based on drug accountability data (number of pills dispensed versus number returned) for ODIN and GS-US-216-0130; while in ARTEMIS, it was derived using the start and stop dates of treatment interruptions (regardless of the reason for the interruption). Both ways of deriving darunavir adherence cover the entire treatment period for each individual patient.

Source: Prezcobix Pharmacoeconomic Evaluation.[32]

Results

The OR for DRV/COBI versus DRV/r (Snapshot algorithm) in the reduced model was 0.878 (95% confidence interval [CI], 0.576 to 1.339). The lower limit of the 95% CI was above the non-inferiority margin on the OR scale. Using the time to loss of virologic response method, the OR was 0.803 (95% CI, 0.534 to 1.208) with the lower limit just above the non-inferiority margin (0.531) (Table 22).

TABLE 22: RESULTS OF UNADJUSTED AND ADJUSTED LOGISTIC REGRESSION ANALYSIS FOR VIROLOGICAL RESPONSE AT 48 WEEKS: DRV/COBI VERSUS DRV/R

	Overall		Naive	
	Snapshot	TLOVR	Snapshot	TLOVR
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Unadjusted	1.287 (0.912 to 1.801)	1.166 (0.831 to 1.636)	[redacted]	[redacted]
Reduced model	0.878 (0.576 to 1.339)	0.803 (0.534 to 1.208)	[redacted]	[redacted]

CI = confidence interval; cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; OR = odds ratio; TLOVR = time to loss of virological response.

Critical Appraisal

The comparative analysis provided by the manufacturer had a number of limitations. The preferred approach to estimating the relative efficacy and safety of DRV/COBI and DRV/r would have been a direct comparative trial. Without such a trial, it is reasonable to attempt an indirect comparison; however, the use of a logistic regression model is not a standard method for doing so. This approach essentially amounts to an observational study–like comparison between single groups from different trials. While attempts were made to control for potential confounders using what appear to be conventional methods for entering and removing variables in logistic regression models, there may be imbalances in unknown or unmeasured population characteristics that could bias the comparison of DRV/COBI with DRV/r. An alternative approach to ensure the DRV/COBI and DRV/r groups were balanced would have been the use of propensity score matching. This method would have been more transparent, and it would have been easier to evaluate whether the groups were balanced.

Without direct comparative trials, indirect comparison and network meta-analysis techniques are preferred approaches for estimating treatment effects, as they allow for randomization within trials to be maintained.[33] While network meta-analyses normally require direct comparative (multi-group) trials that use a common comparator, methods are emerging for the incorporation of data from single-group trials.[34]

The extent to which the findings of the manufacturer's analysis can be applied to treatment-experienced patients is uncertain, given that only 18 such patients were included in study SG 216 0130. Given the small sample size and the resulting loss of precision, it is quite possible that a separate analysis of the treatment-experienced population (had it been performed) would have resulted in estimated ORs with wider CIs and a consequent failure to confirm non-inferiority.

The non-inferiority margin of 12% used in the analysis was consistent with the FDA-recommended non-inferiority margin of 10% to 12% for comparing potent anchor drugs or third-drug regimens in HIV–treatment-naive patients.[35] However, it is unclear if this advice can be extrapolated to a difference between booster drugs such as ritonavir and cobicistat.

While virological response is the main consideration in comparing DRV/COBI with DRV/r, comparative safety is also important. Unfortunately, the manufacturer's analysis did not assess outcomes beyond virological response.

Summary

According to a logistic regression model submitted by the manufacturer, DRV/COBI was found to be non-inferior to DRV/r on virological response at 48 weeks in patients with HIV-1 infection. However, this result should be interpreted with caution given the limitations of the method used, particularly the uncertainty as to whether potential confounders were balanced between the two treatment groups. The applicability of the results to treatment-experienced patients is especially uncertain due to the small number of such patients (N = 18) included in the DRV/COBI trial and the lack of a separate analysis for this population. There were no analyses of comparative safety.

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