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CADTH COMMON DRUG REVIEW

Common Drug Review New Combination Product

DORAVIRINE/LAMIVUDINE/TENOFOVIR DISOPROXIL FUMARATE Fixed-Dose Combination (DELSTRIGO)

Merck Canada Inc.

Indication: A complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults without past or present evidence of viral resistance to doravirine, lamivudine, or tenofovir.

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

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Abbreviations

3TC	lamivudine
BIC	bictegravir
AE	adverse event
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral
cART	combination antiretroviral therapy
CD4	cluster of differentiation 4
CDR	CADTH Common Drug Review
CI	confidence interval
COBI	cobicistat
CTAC	Canadian Treatment Action Council
DHHS	US Department of Health and Human Services
DTG	dolutegravir
DOR	doravirine
DRV	darunavir
DSG	delayed switch group
EFV	efavirenz
EVG	elvitegravir
FAS	full analysis set
FDC	fixed-dose combination
FTC	emtricitabine
HDL-C	high density lipoprotein cholesterol
INSTI	integrase strand transfer inhibitor
ISG	immediate switch group
LDL-C	low-density lipoprotein cholesterol
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PDVF	protocol defined virologic failure
PI	protease inhibitor
RNA	ribonucleic acid
RTV or r	ritonavir
RPV	rilpivirine
RT	reverse transcriptase
SAE	serious adverse event
SOC	standard of care
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate

Drug	doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo)
Indication	As a complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults without past or present evidence of viral resistance to doravirine, lamivudine, or tenofovir
Reimbursement Request	As per indication
Dosage Form(s)	Fixed-dose combination tablet containing doravirine 100 mg, lamivudine 300 mg, and tenofovir disoproxil fumarate 300 mg
NOC Date	November 9, 2018
Manufacturer	Merck Canada Inc.

Executive Summary

Introduction

Human immunodeficiency virus is responsible for causing HIV infection, a condition that gradually weakens the immune system.[1] HIV is transmitted via body fluids such as blood, semen, genital secretions, and breast milk; most commonly from unprotected sexual intercourse or through sharing of contaminated needles and syringes with an infected person.[2] Left untreated, HIV infection can progress to AIDS and ultimately death. Surveillance data from the Public Health Agency of Canada estimates that, at the end of 2016, there were approximately 84,409 people in Canada living with HIV/AIDS, with an incidence rate of 6.4 per 100,000 population, or 2,344 new reported cases yearly.[3] Since the invention of highly active antiretroviral (ARV) therapy in the mid-1990s, antiretroviral therapy (ART) has improved steadily with the availability of newer potent-combination therapies. Treatments are aimed at lowering the level of HIV in the body, thereby allowing the immune system to recover and respond to other infections. Newer ARTs have significantly reduced HIV-associated morbidity and mortality, and HIV is now largely considered a manageable chronic condition.[4]

According to the US Department of Health and Human Services (DHHS)'s "Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV," ARV regimens for treatment-naive patients generally consist of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic enhancer (booster) (cobicistat [COBI] or ritonavir [RTV]).[4] ARV regimens are aimed at the following goals: maximally and durably suppress plasma HIV ribonucleic acid (RNA) below detectable limits (fewer than 50 copies per mL), restore and preserve immunologic function (increase cluster of differentiation 4 cell count), reduce HIV-associated morbidity, prolong the duration and quality of survival, and prevent HIV transmission. For treatment-experienced patients with viral suppression, the DHHS guidelines recommend that selecting a new ARV regimen should be based on the patient's previous ART history, including virologic responses, past ART-associated toxicities and intolerances, resistance test results, drug-drug interactions, and pill burden, in addition other non-clinical considerations.[4]

Current ARTs are not curative; instead, they require lifelong administration and, therefore, high levels of adherence are critical to ensure achievement of treatment goals. To simplify ARV regimens for patients and support long-term adherence, several single-tablet regimens (STRs) are available, alongside other non-STRs, providing clinicians and patients an array of therapeutic options. Delstrigo is a fixed-dose combination of the antiviral drugs doravirine (DOR, 100 mg), lamivudine (3TC, 300 mg), and tenofovir disoproxil fumarate (TDF, 300 mg).[5] Doravirine is an NNRTI of HIV-1, which acts by binding to and blocking HIV reverse transcriptase (RT), an enzyme essential for the HIV replication cycle, thereby preventing HIV from replicating. 3TC is a synthetic nucleoside analogue that inhibits RT via DNA chain termination after incorporation of the nucleotide analogue. TDF is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate, which acts by inhibiting the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Delstrigo can be taken orally once daily with or without food.[5]

The following section provides an overview of the evidence pertaining to the studies relevant for this review. This review was conducted in tandem with an evaluation of the DOR single-dose product, Pifeltro, which includes additional study data that are not presented in this report. Readers are therefore suggested to consult the Pifeltro report for additional context.

Results and Interpretation

Included Studies

Two randomized, active-controlled, noninferiority trials met the inclusion criteria for this systematic review; one double-blind trial (DRIVE-AHEAD, N = 728)[6,7] conducted in treatment-naive patients; and one open-label trial (DRIVE-SHIFT, N = 673)[8] conducted in virologically suppressed patients on a stable ARV regimen. The double-blind and open-label trials had a total follow-up duration of 96 weeks and 48 weeks, respectively. Patients in DRIVE-AHEAD were randomized to receive DOR/3TC/TDF or efavirenz (EFV)/emtricitabine (FTC)/TDF. In DRIVE-SHIFT, patients either immediately switched to DOR/3TC/TDF to be received for 48 weeks (immediate switch group [ISG]) or continued their baseline regimen for 24 weeks (consisting of a RTV- or COBI-boosted PI, or COBI-boosted INSTI, or NNRTI, each administered with two NRTIs) before switching to DOR/3TC/TDF (delayed switch group [DSG]). The primary efficacy outcome in both trials was virologic suppression defined as the proportion of patients with HIV-1 RNA of fewer than 50 copies per mL (calculated using the FDA Snapshot algorithm; i.e., all missing data were treated as failures regardless of the reasons). In DRIVE-AHEAD, the between-treatment difference for the primary efficacy outcome was analyzed at week 48, while in DRIVE-SHIFT the primary analysis compared the proportion of patients maintaining HIV-1 RNA of fewer than 50 copies per mL at 48 weeks for the ISG versus those maintaining this outcome at 24 weeks while on baseline regimen (DSG). The noninferiority margin for the primary outcome was 10% and 8% for the double-blind and open-label trials, respectively. Secondary end points included changes in lipid levels and neuropsychiatric adverse events (AEs). Baseline patient characteristics, and medical and treatment history were largely similar between treatment groups. The majority of the patients were male, with a mean age of 33 years (treatment-naive) and 43 years (treatment-experienced/switch). Overall, 12% to 18% had a history of AIDS, fewer than 5% had hepatitis B and/or C, and 3% to 7% took lipid-lowering therapy. In DRIVE-AHEAD, approximately 20% to 23% had more than 100,000 HIV-1 RNA copies per mL.

Limitations noted in the double-blind trial are as follows: the comparator used in DRIVE-AHEAD, namely the EFV-based fixed-dose combination, is less commonly used in a treatment-naive setting according to the DHHS guidelines. The clinical expert consulted for this review agreed this is also the case for the Canadian context. Additionally, EFV is associated with negative neuropsychiatric events; DOR may therefore demonstrate a favourable neuropsychiatric profile when compared with EFV. Among treatment-naive patients, the rate of discontinuation ranged between 13% and 17% at week 48, and between 18% and 24% at week 96. Notably, the discontinuation rate was higher in the EFV arm compared with the DOR groups. Given that those who discontinued the study (including those who discontinued due to AEs) were considered not to have achieved the primary outcome, the comparative efficacy of DOR may be overestimated.

Several important methodological limitations were noted in the switch trial (DRIVE-SHIFT). First, the primary end point used in the switch trial was not consistent with the latest issue of FDA recommendations for HIV drugs. According to this, the primary efficacy outcome for switch trials should be HIV-1 RNA of 50 copies per mL or more, given that the end point is focused on patients who lose virologic control as a result of switching from a stable, virologically suppressive regimen to another regimen.[9] However, DRIVE-SHIFT was initiated before the new recommendations were published. For the primary efficacy end point, the noninferiority margin chosen for DRIVE-SHIFT (8%) was more stringent than the 10% recommended by the FDA, which was used in DRIVE-AHEAD. However, there is some uncertainty regarding whether the 8% noninferiority margin for the primary outcome in DRIVE-SHIFT was actually met, given that the FDA Snapshot algorithm to account for missing data (missing data equals failure) was not followed properly. Instead, some patients with missing data at week 48 had their blood samples reanalyzed from other sources and their data were added to the analyses data set post-hoc. Following this modification, the noninferiority margin was met for the primary efficacy outcome; however, noninferiority was not demonstrated with the true FDA Snapshot approach initially. Finally, analysis of the primary end point was based on an unequal period of exposure to the respective study drugs (DOR/3TC/TDF or baseline regimens). Patients in the ISG group received DOR for 48 weeks, whereas those in the DSG group received their baseline regimens for 24 weeks followed by DOR/3TC/TDF for 24 weeks. Statistical comparisons were not made between the treatment groups at week 24 for most end points (including the primary efficacy end point), or were not controlled for multiplicity. Instead, results for the ISG group at week 48 were compared with the DSG group at week 24 in many cases.

Efficacy

All efficacy analyses were conducted in the full analyses set, a modified intention-to-treat population, which consisted of all randomized patients who received at least one dose of the study medication and had at least one measurement of the outcome (baseline or post-baseline).

Among treatment-naive patients, the primary outcome (proportion of patients with HIV-1 RNA of fewer than 50 copies per mL at week 48) was achieved by 84.3% and 80.8% patients receiving DOR/3TC/TDF and EFV/FTC/TDF in DRIVE-AHEAD, respectively. The between-treatment difference was 3.5% (95% confidence interval [CI], −2.0 to 9.0), meeting the pre-specified noninferiority margin of 10%, given that the lower bound of the 95% CI for treatment differences were above −10 percentage points. The proportions of patients with virologic success at week 96 were 77.5% and 73.6% for patients receiving DOR/3TC/TDF and EFV/ FTC/TDF, respectively.

The proportions of treatment-naive patients with HIV-1 RNA of 50 copies per mL or more (virologic failure) using the FDA-defined Snapshot approach were similar between the DOR/3TC/TDF and EFV/FTC/TDF groups; 10.7% versus 10.2%, respectively, at week 48, and 15.1% versus 12.1%, respectively, at week 96. No formal statistical testing was conducted at either time point.

In DRIVE-SHIFT, the proportion of patients with HIV-1 RNA of fewer than 50 copies per mL was 90.8% at week 48 in the ISG group compared with 94.6% in the DSG group at week 24; with a treatment difference of −3.8% (95% CI, −7.9 to 0.3). Given that the lower bound of the 95% CI was not less than −8%, switching to DOR/3TC/TDF was considered noninferior to continued treatment with baseline regimen. However, DRIVE-SHIFT had a number of methodologic issues leading to questionable validity with respect to establishing comparative efficacy between switching to DOR/3TC/TDF versus staying on baseline regimens. The comparison of virologic suppression between groups based on different durations of follow-up is unusual and the CADTH Common Drug Review review team is uncertain of the impact this has on the results. However, between-treatment comparisons based on the same duration of follow-up would have more internally validity. The between-treatment difference for the proportion of patients with HIV-1 RNA of fewer than 50 copies per mL at the same time point in each group (24 weeks) was −0.9% (95% CI, −4.7 to 3.0), statistical testing was not controlled for multiplicity. Further, based on guidance from the FDA, the appropriate end point for treatment-switch trials is the proportion of patients with HIV-1 RNA of 50 copies per mL or more with an associated noninferiority margin of 4%. The proportions of patients with HIV-1 RNA of 50 copies per mL or more were similar between the ISG and DSG at weeks 48 and 24 (1.6% and 1.8% respectively), and between the ISG and DSG at week 24 for each group (1.8% in both groups); between-treatment differences were −0.2 (95% CI, −2.5 to 2.1) and −0.0 (95%CI, −2.3 to 2.3), respectively; however, statistical testing was not controlled for multiplicity.

Harms

The frequency of AEs at week 96 was similar between the treatment groups in the double-blind trials: 88.2% versus 93.1% among patients receiving DOR and EFV, respectively, in DRIVE-AHEAD. In the switch trial, 80.3% of patients in the ISG group receiving DOR through week 48 experienced AEs. A higher proportion of treatment-switch patients receiving DOR reported AEs at week 24; a pattern consistent with the notion that patients switching therapies are likely to experience more AEs versus those remaining on their baseline therapy: 68.9% versus 52.5% among patients receiving DOR and baseline regimens, respectively; and 60.3% of patients in the DSG group experienced AEs post-switching (i.e., between weeks 24 and 48).

Among treatment-naive patients, serious AEs were reported by 5.8% to 8.2% of patients receiving DOR and EFV, respectively. Among treatment-switch patients, 1% to 5% patients across treatment groups reported serious AEs. The proportions of patients who withdrew from the study due to AEs were generally low, ranging from 3% to 7% in treatment-naive patients and 0% to 4% in treatment-switch patients. A total of eight deaths were reported in the two trials; one of which (cause of death: myocardial infarction; patients was in DRIVE-SHIFT and receiving DOR) was attributed to the study drug, although no confirmatory diagnosis (diagnosis by a medical professional or autopsy) was done.

DOR was associated with fewer neuropsychiatric AEs; however, the benefits were largely seen in comparison with EFV in DRIVE-AHEAD, which is commonly associated with neuropsychiatric side effects. Of note, the clinical expert consulted for this review indicated that an ARV formulation with tenofovir alafenamide fumarate as the backbone is more desirable to clinicians and patients, given that it is associated with less bone and renal toxicity.

Potential Place in Therapy[1]

Doravirine, an NNRTI, has some positive attributes compared with its predecessors in the class, including the lack of neuropsychiatric side effects (compared with efavirenz), lack of requirement to be taken with food and with normal gastric acidity (unlike rilpivirine), and once-daily dose (unlike etravirine).

Its role will be limited by its late entry into the market. As a single daily dose "third component" of an antiretroviral combination, it has been preceded to market by rilpivirine, dolutegravir, and boosted darunavir, among others. As a co-formulated STR, Delstrigo (DOR/3TC/TDF) is one of almost a dozen available single-tablet options, including Atripla (and generics), Complera, Odefsey, Stribild, Genvoya, Triumeq, Biktarvy, Symtuza, and Juluca.

The most commonly prescribed antivirals for treatment-naive patients, or those switching for reasons of convenience or tolerance, are the STRs, and in particular, Genvoya and Triumeq. Although having their own idiosyncracies, most of these are well tolerated, convenient, and effective. Use of the doravirine STR would be infrequent, as the tenofovir component of this Delstrigo STR is the TDF formulation, which is associated with renal and bone toxicities. The newer tenofovir alafenamide formulation, found in Biktarvy and Genvoya, is not associated with these side effects and is generally preferred by prescribing physicians.

As a single component of a regimen, doravirine (Pifeltro) would be a very reasonable treatment consideration if an STR is not available or an option for the individual patient. Most likely, it would be used where a tenofovir-containing regimen is not considered ideal, and where side effects on Triumeq have occurred. It would most likely be used with Kivexa (or its generic counterpart). I would anticipate its use to be infrequent.

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

Conclusions

Results from one double-blind randomized controlled trial in treatment-naive patients demonstrates that DOR/3TC/TDF is noninferior to EFV/FTC/TDF in achieving virologic suppression (HIV-1 RNA of fewer than 50 copies per mL) at week 48. Differential study discontinuation may have biased the estimates of comparative efficacy toward DOR/3TC/TDF, but the impact is unlikely to change the conclusion of noninferiority. DOR/3TC/TDF was associated with fewer neuropsychiatric events compared with EFV/FTC/TDF; however, the latter STR is known for its neuropsychiatric effects due to its EFV component. There is a lack of high-quality evidence of the efficacy and safety of DOR/3TC/TDF compared with other newer, more frequently used regimens, including STRs.

Results from one open-label randomized controlled trial in virologically suppressed treatment-experienced patients suggest that DOR/3TC/TDF is noninferior to continuing baseline treatment (consisting of an RTV- or COBI-boosted PI, or COBI-boosted INSTI, or NNRTI, each administered with two NRTIs) based on the primary outcome of HIV-1 RNA of fewer than 50 copies per mL. However, this finding is of questionable validity given that the two treatment arms had an unequal period of exposure to the respective study drugs. Additionally, the FDA-recommended end point of interest for switch trials (HIV-1 RNA of 50 copies per mL or more) was not included in the statistical hierarchy.

1. Product Information

1.1 Health Canada–Approved Indications

Indication(s) to be Reviewed by CADTH
Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate) is indicated as a complete regimen for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to doravirine, lamivudine, or tenofovir.

1.2 Requested Listing Criteria

Requested Listing Criteria
As per indication.

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

1.3.1 Rationale

HIV infection is treated with combination (c) ART (ART); the goal of cART is to suppress viral load, thereby decreasing infectivity and preventing HIV transmission.[2] Given that there is no cure for HIV, patients must continue cART for life to maintain virologic response and retain the benefits of treatment.[2-4]

As patients with HIV live longer and receive cART for several decades, they are exposed to an increased risk of various ART/HIV-associated and non-HIV related comorbidities.[5-10] Patients must therefore deal with polypharmacy, not only for the treatment of HIV itself, but also for management of comorbidities.[1,11,12] Polypharmacy leads to an increased pill burden, greater risk of drug-drug interactions, and more drug-related adverse events (AEs), which may in turn result in nonadherence to ART and potentially compromise ART efficacy.[1,12] Along with being more likely to have multiple comorbidities and associated polypharmacy, older patients are also more likely to experience ART-related AEs and they may be particularly susceptible to cognitive impairments and depression.[13,14] These factors may all further contribute to poor ART adherence.[15]

The most common treatment-specific reasons for switching ARTs include regimen simplification (33%), toxicity (31%), virologic failure (6%), and drug interactions (4%).[16] Simplifying antiretroviral (ARV) regimens and reducing toxicity are key strategies used to increase ART adherence and improve HIV virologic outcomes.[17-20] Single-tablet regimens (STRs) given once daily allow for the simplification of the ART regimens, reduction in pill burden, improvement of ART adherence, quality of life and patient preferences which may ensure long-lasting efficacy and durability of ART.[18]

With the newly attainable aging of the HIV-positive population, patient comorbidities, polypharmacy, and cumulative toxicities of ART become more and more important in therapy decisions.[1] Treatment guidelines consistently underscore the importance of simplifying and customizing the ARV regimen for the individual patient by considering the specifics of their clinical situation.[2] For all these reasons, there is a continuous and ongoing need for diversity of ART options, available both as single-agent and combined (STR)

formulations, and for new options that bring clinical advantages over the preceding generation that do not interact with other chronic medications or exacerbate comorbidities.[1,2]

1.3.2 Place in Therapy

Per the anticipated indication, doravirine (DOR) STR should be used for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to DOR, lamivudine (3TC), or tenofovir. DOR STR tablets are available as a fixed-dose combination of 100 mg of DOR, 300 mg of 3TC, and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage regimen of DOR STR is one tablet taken orally once daily with or without food.

DOR STR can be used for initiating therapy in patients with HIV-1 who are naive to ART or for patients with HIV-1 who have failed on their current ART (due to tolerance, AEs, resistance, and so forth). Both 3TC and TDF are widely used “backbone” therapies for the treatment of HIV-1. The combination of DOR and these two nucleoside reverse transcriptase inhibitors (NRTIs) (at their most commonly prescribed doses) simplifies the administration of cART with the goal of increasing reducing pill burden and improving adherence of ART.

CADTH Common Drug Review (CDR) reviewer comment: While the manufacturer indicates that common reasons for switching include virologic failure, and that Delstrigo could be initiated in patients who have failed on their current regiment (due in some cases to resistance), it should be noted that, in the one trial that enrolled treatment-experienced patients, all patients were virologically suppressed on their current regimen. Thus, there is no randomized controlled trial evidence for the use of Delstrigo in patients who have failed their current therapy as evidenced by HIV-1 ribonucleic acid (RNA) of 50 copies per mL or more, whether due to resistance or other reasons.

1.3.3 Dosing Considerations

DOR STR can be used for initiating therapy in patients with HIV-1 who are naive to ART or for patients with HIV-1 who have failed on their current ART (due to tolerance, AEs, resistance, and so forth). As DOR STR is only available as one fixed-dose combination of 100 mg of DOR, 300mg of 3TC, and 300mg of TDF, there is no ability to titrate doses of DOR STR, and increasing the dose of one component dose not result in an unnecessary dose increase of the other component.

CDR reviewer comment: As previously mentioned, there is no randomized controlled trial evidence for the use of Delstrigo in patients who have failed their current therapy as evidenced by HIV-1 RNA of 50 copies per mL or more, whether due to resistance or other reasons. It is unlikely that treatment-naive or treatment-experienced patients would be initiated on the individual components of Delstrigo, given that this would require the use of three individual dosage formulations.

2. Clinical Evidence

2.1 Pivotal Clinical Studies

The DOR/3TC/TDF fixed-dose combination (FDC) clinical program assessed the safety and efficacy of DOR in combination with 3TC and TDF, as an FDC, in patients who were both naive to ART and in patients who were switched from existing ART.

The following are pivotal clinical trials supporting DOR STR. These studies can also be found in the Clinical Studies section of the submission.

CDR reviewer comment: Although the manufacturer included three clinical trials in this report, only in DRIVE-AHEAD and DRIVE-SHIFT did patients receive the DOR/3TC/TDF STR relevant to this review. In the DRIVE-FORWARD study, patients received DOR in combination with other NRTI backbone therapies; therefore, this is not a pivotal trial for Delstrigo. Thus, the CDR team will focus on reviewing and appraising the evidence pertaining to DRIVE-AHEAD and DRIVE-SHIFT.

Table 1: Pivotal Clinical Studies

Study Name	Design	Objectives	Population
DRIVE-AHEAD A phase III, multi-centre, double-blind, randomized, active comparator-controlled clinical trial to evaluate the safety and efficacy of MK-1439A once daily versus Atripla once daily in treatment-naive HIV-1–infected patients.	A phase III, multi-centre, double-blind, randomized, active comparator-controlled, 96-week[a] clinical trial with a 96-week extension. A total of 734 participants were randomized 1:1 to doravirine 100 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg or efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg.	**Primary efficacy end point**: Proportion of participants with HIV-1 RNA < 50 copies/mL at week 48. **Key secondary efficacy end points:** Proportion of participants with HIV-1 RNA < 50 copies/mL at week 96. Change from baseline in CD4 T-cell count at week 48 and 96. • Proportion of participants with HIV-1 RNA < 40 copies/mL at week 48 and 96.	Adults (aged ≥ 18 years) with HIV-1 infection who were naive to ART, with plasma HIV-1 RNA ≥ 1000 copies/mL within 45 days prior to the treatment phase of the study, alkaline phosphatase concentrations three times the upper limit of normal or less, aminotransferase concentrations five times the upper limit of normal or less, a creatinine clearance rate of 50 mL/min or higher at the time of screening, and no documented or known resistance to any of the study regimen components.
DRIVE-SHIFT A phase III, multi-centre, open-label, randomized study to evaluate a switch to MK-1439A in HIV-1-infected subjects virologically suppressed on a stable regimen of a ritonavir- or cobicistat-boosted protease inhibitor, or cobicistat-boosted integrase strand transfer inhibitor, or	A phase III, multi-centre, open-label, randomized study over 48 weeks. A total of 673 patients were randomized 1:1 to switch on day 1 from their existing ART or at week 24 from their existing ART to doravirine 100 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg FDC.	**Primary end point:** Proportion of patients maintaining HIV-1 RNA < 50 copies/mL at week 48 in the immediate switch group and at week 24 in the delayed switch group. **Key secondary end points:** Change from baseline in fasting serum LDL-C and non-HDL-C. Proportion of patient maintaining HIV-1 RNA < 40 copies/mL. Change from baseline in CD4 cell count.	Adults (aged ≥ 18 years) with HIV-1 infection and who have had HIV-1 RNA < 40 copies/mL for at least 6 months on a stable EVG/COBI–, PI/COBI, or RTV- or NNRTI-based ARV regimen, not taking lipid-lowering medications, alkaline phosphatase concentrations three times the upper limit of normal or less, aminotransferase concentrations five times the upper limit of normal or less, a creatinine clearance rate of 50 mL/min or higher at the time of screening and no known resistance to any of the study agents.

Study Name	Design	Objectives	Population
non-nucleoside reverse transcriptase inhibitor; each administered with two nucleoside/nucleotide reverse transcriptase inhibitors.[b]			
DRIVE-FORWARD Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1: 48-week results of a randomized, double-blind, phase III, noninferiority trial.	Multi-centre, randomized, controlled, double-blind, noninferiority trial. Randomization (1:1) was stratified by plasma HIV-1 RNA count (≤ 100,000 or > 100,000 copies/mL) at screening and by the NRTI component, which was selected by the investigator. Base study of blinded treatment for 96 weeks followed by open-label study extension for additional 96 weeks.	**Primary efficacy end point:** Proportion of participants with HIV-1 RNA < 50 copies/mL at week 48. **Key secondary efficacy end points:** Proportion of participants with HIV-1 RNA < 50 copies/mL at week 96. Change from baseline in CD4 T-cell count at week 48 and 96 Proportion of participants with HIV-1 RNA < 40 copies/mL at week 48 and 96.	Adults (aged ≥ 18 years) with HIV-1 infection who were naive to ART, with plasma HIV-1 RNA ≥ 1,000 copies/mL within 45 days prior to the treatment phase, alkaline phosphatase concentrations three times the upper limit of normal or less, aminotransferase concentrations five times the upper limit of normal or less, a creatinine clearance rate of 50 mL/min or higher at the time of screening, and no documented or known resistance to any of the study regimen components.

ART = antiretroviral therapy; COBI = cobicistat; CD4 = cluster of differentiation 4; EVG = elvitegravir; FDC = fixed-dose combination; HDL-C = high density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RNA = ribonucleic acid; RTV = ritonavir.

Note: CDR reviewer comment: The manufacturer frequently uses the name "MK-1439A" to refer to the Delstrigo product.

[a] The duration of the DRIVE-AHEAD study was changed from 48 to 96 weeks based on data from the Orkin et al.[10]

[b] Data were added or modified by the CADTH Common Drug Review reviewer based on data from the clinical study report.[8]

DRIVE-AHEAD (PN-021)

A. Study Characteristics

DRIVE-AHEAD is a phase III, double-blind, noninferiority trial. ARV treatment-naive adults with 1,000 HIV-1 RNA copies per mL or more were randomized (1:1) to once-daily, fixed-dose DOR at 100 mg, 3TC at 300 mg, and TDF at 300 mg (DOR/3TC/TDF) or to efavirenz (EFV) at 600 mg, emtricitabine (FTC) at 200 mg, and TDF at 300 mg (EFV/ FTC/TDF) for 96 weeks. The primary efficacy end point was the proportion of participants with fewer than 50 HIV-1 RNA copies per mL at week 48 (FDA Snapshot approach; noninferiority margin 10%).

Table 2: Details of DRIVE-AHEAD[a]

Characteristics		DRIVE-AHEAD
Study Design	**Objective**	Pivotal efficacy and safety study
	Blinding	Double blind
	Study period	2015-06 to 2017-03
	Study centres	Australia (2), Belgium (3), Canada (4), Chile (4), Columbia (3), Denmark (2), Germany (6), Guatemala (4), Honduras (1), Israel (2), Mexico (3), New Zealand (1), Peru (7), Portugal (5), Puerto Rico (3), Russia (8), South Africa (9), Spain (4), Switzerland (3), Taiwan (6), Thailand (6), UK (7), US (31)
	Design	Noninferiority trial vs. efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg
Study Population	**Randomized (N)**	734
	Inclusion criteria	• Adults (≥18 years of age) HIV-1 positive as determined by a positive result on an enzyme-immunoassay, has screening plasma HIV-1 RNA (determined by the central laboratory) ≥ 1,000 copies/mL within 45 days prior to the treatment phase of this study, and has HIV treatment indicated based on physician assessment • Has never received ART • No documented or known resistance to any of the study drugs • Is highly unlikely to either become pregnant or impregnate a partner
	Exclusion criteria	• Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound results of the study • Is a user of recreational or illicit drugs or has a recent history of alcohol/drug abuse • Has been treated for a viral infection other than HIV-1 (e.g., hepatitis B) with an agent that is active against HIV-1 • Has participated in a study with an investigational drug/device within 30 days prior to screening • Has used systemic immunosuppressive therapy or immune modulators within 30 days prior to treatment in this study or is anticipated to need them during the course of the study • Has a current (active) diagnosis of acute hepatitis due to any cause (note: participants with chronic hepatitis B and C may enter the study as long as they fulfill all entry criteria, have stable liver function tests, and have no significant impairment of hepatic synthetic function) • Is a female who is pregnant, breastfeeding, or expecting to conceive • Is a female and is expecting to donate eggs or is male and is expecting to donate sperm (investigators will provide appropriate guidance regarding egg and/or sperm donation after completion of the study treatment regimen) • Has evidence of decompensated liver disease manifested by the presence of or a history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy or other signs or symptoms of advanced liver diseases, or has liver cirrhosis and a Child-Pugh Class C score or Pugh-Turcotte score > 9
Drugs	**Intervention**	Dosing regimen for 96 weeks, once-daily oral dose of: • doravirine 100 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg as a STR plus comparator placebo
	Comparator(s)	• efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg as a STR plus comparator placebo
Duration	**Run-in**	45 days
	Treatment	96 weeks
	Extension (OL)	96 weeks

Characteristics		DRIVE-AHEAD
Outcomes	**Primary end point(s)**	Percentage of patients achieving HIV-1 RNA < 50 copies/mL at 48 weeks
	Other end points	• Change from baseline in fasting low-density lipoprotein cholesterol (LDL-C) • Change from baseline in fasting non-high-density lipoprotein cholesterol (non-HDL-C) • Change from baseline in cluster of differentiation (CD4) cell counts • Percentage of participants achieving HIV-1 RNA < 40 copies/mL or < 200 copies/mL • Percentage of participants with HIV-1 RNA >=50 copies/mL • Percentage of participants achieving HIV-1 RNA < 50 copies/mL at week 96 • Percentage of patients with dizziness, sleep disorders, and disturbances, or with altered sensorium
Notes	**Publications**	Clinicaltrials.gov identifier: NCT02403674 Orkin C et al., Clin Infect Dis. 2018 Aug 31, (Epub ahead of print)[10]

ART = antiretroviral therapy; CD4 = cluster of differentiation 4; OL = open label; RNA = ribonucleic acid; STR = single-tablet regime; vs. = versus.

[a] Data were added or modified by the CADTH Common Drug Review reviewer based on data from the clinical study report.[6,7]

Intervention and Comparators

Participants were randomly assigned (1:1) to either DOR/3TC/TDF (plus placebo for EFV/FTC/TDF) or EFV/FTC/TDF (plus placebo for DOR/3TC/TDF), stratified by screening HIV-1 RNA (either ≤ or > 100,000 copies per mL) and chronic hepatitis B and/or C coinfection (either yes or no). DOR/3TC/TDF (and matching placebo) were taken orally once daily, without regard to food, at approximately the same time each day. EFV/FTC/TDF (and matching placebo) were taken orally once daily at bedtime on an empty stomach. No dose modifications were permitted during the study.

Outcomes

Efficacy

Plasma HIV-1 RNA was measured at all study visits by the central laboratory using the Abbott RealTime HIV-1 assay (lower limit of quantification of 40 copies per mL). Protocol defined virologic failure (PDVF) consisted of virologic rebound (confirmed HIV-1 RNA of 50 copies per mL or more after initial response of HIV-1 RNA of fewer than 50 copies per mL at any time during the study) or non-response (either confirmed HIV-1 RNA of 200 copies per mL or more at week 24 or 36 or confirmed HIV-1 RNA of 50 copies per mL or more at week 48). In all cases, confirmation required two consecutive measures of HIV-1 RNA at least one week apart. Participants who met PDVF criteria were discontinued from the study, regardless of their adherence to the study therapy.

Safety

Safety was monitored by AE reporting, treatment-emergent abnormalities in laboratory tests, and physical examinations. AEs were assessed by the investigator for intensity (mild, moderate, severe), seriousness, and relationship to study therapy. Laboratory values were graded according to the Division of AIDS criteria.

Statistical Analyses

The primary efficacy population was the full analysis set (FAS), which consisted of all randomized participants who received at least one dose of a study drug. The primary efficacy end point was the proportion of participants achieving HIV-1 RNA of fewer than 50 copies per mL at week 48 using the FDA Snapshot approach, which treats all missing values as failures, regardless of the reason. The difference between treatment groups at

each time point and the associated 95% confidence intervals (CIs) were calculated using the stratum-adjusted Mantel–Haenszel method. The pre-specified noninferiority margin was −10%. With 340 participants per treatment arm, the trial had 90% power to demonstrate that DOR/3TC/TDF is noninferior to EFV/FTC/TDF on the primary end point, at the one-sided 2.5% alpha level, assuming a true response rate of 80% for both arms.

CDR reviewer comment: The following outcomes were tested in the given order as part of the statistical testing hierarchy; proportion of patients achieving HIV-1 RNA of fewer than 50 copies per mL at week 48, neuropsychiatric AEs (three categories; i.e., dizziness, sleep disorders and disturbances, or with altered sensorium) at week 48, mean change from baseline for fasting low-density lipoprotein cholesterol (LDL-C) at week 48, mean change from baseline for fasting non-high density lipoprotein cholesterol (HDL-C) at week 48, and proportion of patients achieving HIV-1 RNA of fewer than 50 copies per mL at week 48.

B. Results

Baseline Characteristics

Demographics and baseline characteristics were generally similar between the treatment groups (Table 3). By week 48, 14% of the DOR/3TC/TDF group and 17% of the EFV/FTC/TDF group had discontinued study treatment, primarily due to lack of efficacy, AEs, withdrawal of consent, and loss to follow-up.

No significant conditions, medications, or relevant issues to note.

Table 3: Baseline Characteristics of DRIVE-AHEAD

	DOR/3TC/TDF	EFV/FTC/TDF	Total
	(N = 364)	(N = 364)	(N = 728)
Age (years), median (range)	32.0 (18, 70)	30.0 (18, 69)	31.0 (18, 70)
Male, n (%)	305 (84%)	311 (85%)	616 (85%)
Race, n (%)			
White	177 (49%)	170 (47%)	347 (48%)
Black or African-American	67 (18%)	68 (19%)	135 (19%)
Asian	59 (16%)	65 (18%)	124 (17%)
Other[a]	61 (17%)	61 (17%)	122 (17%)
Hispanic or Latino ethnicity	126 (35%)	120 (33%)	246 (34%)
Region, n (%)			
Africa	37 (10%)	27 (7%)	64 (9%)
Asia/Pacific	59 (16%)	62 (17%)	121 (17%)
Europe	88 (24%)	94 (26%)	182 (25%)
Latin America	89 (24%)	87 (24%)	176 (24%)
North America	91 (25%)	94 (26%)	185 (25%)
CD4+ T-cell count			
Median (range), cells/mm^3	414 (19, 1399)	388 (19, 1452)	397 (19, 1452)
≤ 200 cells/mm^3, n (%)	44 (12%)	46 (13%)	90 (12%)
> 200 cells/mm^3, n (%)	320 (88%)	318 (87%)	638 (88%)
Plasma HIV-1 RNA			

	DOR/3TC/TDF	EFV/FTC/TDF	Total
	(N = 364)	(N = 364)	(N = 728)
Median (range), log_{10} copies/mL	4.4 (2.4 to 6.1)	4.5 (2.6 to 6.4)	4.4 (2.4 to 6.4)
≤ 100 000 copies/mL, n (%)	291 (80%)	282 (77%)	573 (79%)
> 100 000 copies/mL, n (%)	73 (20%)	82 (23%)	155 (21%)
History of AIDS, n (%)	46 (13%)	53 (15%)	99 (14%)
Hepatitis B and/or C,[b] n (%)	11 (3%)	9 (2%)	20 (3%)
HIV-1 subtype B, n (%)	232 (64%)	253 (70%)	485 (67%)

DOR/3TC/TDF = doravirine at 100 mg, lamivudine at 300 mg, and tenofovir disoproxil fumarate at 300 mg; EFV/FTC/TDF = efavirenz at 600 mg, emtricitabine at 200 mg, and tenofovir disoproxil fumarate at 300 mg; CD4 = cluster of differentiation 4; RNA = ribonucleic acid.

[a] Other race includes multiracial, American Indian, or Alaska Native.

[b] Evidence of hepatitis B surface antigen or hepatitis C virus RNA.

Patient Disposition

The most common reasons for screen failure were a documented or known resistance to any study drug (n = 139) and plasma HIV-1 RNA of fewer than 1,000 copies per mL at screening (n = 62). Of 992 participants screened, ~2.4% were excluded due to DOR-associated mutations (Y188L and V106I) and ~4.0% were excluded due to EFV-associated mutations (Y188L, K103N, L100I, K101, V108I, G190, and Y181C).

Patient disposition from the 48-week treatment period is shown in Table 4.

Table 4: Summary of Patient Disposition for DRIVE-AHEAD (Week 48)

Disposition	DOR/3TC/TDF	EFV/FTC/TDF
Screened, N	992	
Randomized, N	734	
Discontinued, N (%)	51 (13.9%)	61 (16.7%)
WDAEs, N (%)	10 (2.7%)	23 (6.3%)
Withdrawal due to SAEs, N (%)	0 (0%)	0 (0%)
Lost to follow-up, N (%)	6 (1.6%)	7 (1.9%)
Lack of efficacy, N (%)[a]	18 (4.9)	10 (2.7)
Other reason, N (%)[a]	17 (4.6)	21 (5.7)
Intention to treat, N	368	366
Full analysis set,[a] N	364	364
Per protocol, N	NA	NA
Safety, N	364	364

DOR/3TC/TDF = doravirine at 100 mg, lamivudine at 300 mg, and tenofovir disoproxil fumarate at 300 mg; EFV/FTC/TDF = efavirenz at 600 mg, emtricitabine at 200 mg, and tenofovir disoproxil fumarate at 300 mg; NA = not applicable; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Data added or modified by the CADTH Common Drug Review reviewer based on Orkin 2018.[10]

CDR reviewer comment: Full disposition details for week 48 and 96 for DRIVE-AHEAD are included in the Pifeltro CDR Clinical Review Report.

Efficacy

Table 5: Efficacy Results for DRIVE-AHEAD (Week 48)

	DOR/3TC/TDF (N = 364)		EFV/FTC/TDF (N = 364)	
Primary analysis (FDA Snapshot approach)	n	(%)	n	(%)
HIV-1 RNA < 50 copies/mL	307	(84.3)	294	(80.8)
HIV-1 RNA ≥ 50 copies/mL[a]	39	(10.7)	37	(10.2)
No virologic data in week 48 window	18	(4.9)	33	(9.1)
Discontinued study due to AE or death[b]	9	(2.5)	24	(6.6)
Discontinued study for other reasons[c]	9	(2.5)	8	(2.2)
On study but missing data in window	0	(0.0)	1	(0.3)
Secondary and exploratory end points	n/N	(%)	n/N	(%)
HIV-1 RNA < 50 copies/mL (observed failure)	307/346	(88.7)	294/331	(88.8)
HIV-1 RNA < 40 copies/mL (FDA Snapshot)	305/364	(83.8)	290/364	(79.7)
HIV-1 RNA < 200 copies/mL (FDA Snapshot)	313/364	(86.0)	301/364	(82.7)

AE = adverse event; DOR/3TC/TDF = doravirine at 100 mg, lamivudine at 300 mg, and tenofovir disoproxil fumarate at 300 mg; EFV/FTC/TDF = efavirenz at 600 mg, emtricitabine at 200 mg, and tenofovir disoproxil fumarate at 300 mg; RNA = ribonucleic acid.

[a] Includes participants who changed any component of background therapy before week 48, participants who discontinued study drug before week 48 for lack or loss of efficacy, and participants with HIV-1 RNA of 50 copies per mL or more in the week 48 window (relative day 295 to 378).

[b] Includes participants who discontinued because of AE or death at any time point from day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[c] Other reasons include: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, screen failure, and withdrawal by participant.

DOR/3TC/TDF was noninferior to EFV/FTC/TDF on the primary efficacy end point, with 84.3% (307 out of 364) and 80.8% (294 out of 364) of participants, respectively, achieving HIV-1 RNA of fewer than 50 copies per mL at week 48 (difference, 3.5%; 95% CI, –2.0 to 9.0). Virologic response rates were similar between the treatment groups at each time point and across all baseline prognostic and demographic factors except age, with response rates favouring EFV/FTC/TDF in participants 31 years old or younger and DOR/3TC/TDF in those older than 31. Among participants with high baseline HIV-1 RNA (more than 100,000 copies per mL), 56 out of 69 (81.2%) in the DOR/3TC/TDF group and 59 out of 73 (80.8%) in the EFV/FTC/TDF group achieved HIV-1 RNA of fewer than 50 copies per mL at week 48. Similar results were observed for the virologic end points of HIV-1 RNA of fewer than 40 copies per mL (83.8% for DOR/3TC/TDF versus 79.7% for EFV/FTC/TDF; difference, 4.1%; 95% CI, –1.5 to 9.7) and HIV-1 RNA of fewer than 200 copies per mL. The mean change in CD4+ T-cell count from baseline to week 48 was similar in the DOR/3TC/TDF and EFV/FTC/TDF groups (198 versus 188 cells/mm^3; difference, 10.1; 95% CI, –16.1 to 36.3).

CDR reviewer comment: Additional efficacy outcomes at week 48 and week 96 are summarized in the CDR Clinical Review Report for Pifeltro.

DRIVE-SHIFT (PN-024)

A. Study Characteristics

(See Merck Sharp & Dohme Corp. 2018. A Phase III Multi-center, Open-Label, Randomized Study to Evaluate a Switch to MK-1439A in HIV-1-Infected Subjects Virologically Suppressed on a Regimen of a Ritonavir-boosted Protease Inhibitor and Two Nucleoside Reverse Transcriptase Inhibitors (NRTIs). PN-024, section 12 – Safety Evaluation, page 99).[8]

A phase III, multi-centre, open-label, randomized (2:1 - DOR/3TC/TDF: current therapy) study to evaluate a switch to DOR/3TC/TDF in HIV-1-infected patients virologically suppressed on a regimen of a ritonavir (RTV)-boosted protease inhibitor (PI) and two NRTIs. The protocol was subsequently amended to include switches from cobicistat [COBI]-boosted PIs, COBI-boosted elvitegravir (EVG), or non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Table 6: Study Details for DRIVE-SHIFT[a]

Characteristics		Details for DRIVE-SHIFT
Study Design	Objective	Pivotal efficacy and safety study
	Blinding	Open label
	Study period	2015-06 to 2018-02
	Study centres	Argentina (4), Australia (4), Austria (3), Belgium (5), Canada (5), Colombia (1), Denmark (4), France (4), Germany (7), Guatemala (2), Israel (7), Italy (10), Mexico (3), New Zealand (1), Peru (1), Poland (3), Puerto Rico (3), Russia (6), South Korea (2), Spain (8), Switzerland (4), UK (9), US (38)
	Design	Noninferiority
Study Population	Randomized (N)	673
	Inclusion criteria	• Clinically stable HIV-1 infected adults (≥ 18 years) who were virologically suppressed for ≥ 6 months, had HIV-1 RNA levels < 40 copies/mL at screening and were on a stable ART regimen consisting of one of the following: ritonavir- or cobicistat-boosted protease inhibitor (atazanavir, darunavir, or lopinavir) or cobicistat-boosted elvitegravir or an NNRTI (specifically, efavirenz, nevirapine, or rilpivirine) in combination with two NRTIs (and no other antiretroviral therapy) continuously for >= 6 months • Receiving first or second retroviral regimen (participants receiving a NNRTI at screening must be on their first retroviral regimen) • No history of using an experimental NNRTI • Not receiving lipid-lowering therapy or on a stable dose of lipid-lowering therapy at the time of enrolment • Male or female participant not of reproductive potential or, if of reproductive potential, agrees to avoid becoming pregnant or impregnating a partner while receiving study drug and for 14 days after the last dose of study drug by complying with one of the following: 1) practice abstinence from heterosexual activity, or 2) use acceptable contraception during heterosexual activity
	Exclusion criteria	• Uses recreational or illicit drugs or has a recent history of drug or alcohol abuse or dependence • Received treatment for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1 such as adefovir, emtricitabine, lamivudine, or tenofovir • Has documented or known resistance to study drugs including MK-1439, lamivudine, and/or tenofovir • Participated in a study with an investigational compound or device within 30 days or anticipates doing so during the course of this study • Used systemic immunosuppressive therapy or immune modulators within 30 days or anticipates needing them during the course of this study (short courses of corticosteroids will be allowed) • Current, active diagnosis of acute hepatitis due to any cause (participants with chronic hepatitis B and

Characteristics		Details for DRIVE-SHIFT
		C may enter the study as long as they fulfill all entry criteria, have stable liver function tests, and have no significant impairment of hepatic function) • Has evidence of decompensated liver disease or has liver cirrhosis and a Child-Pugh Class C score or Pugh-Turcotte score > 9 • Pregnant, breastfeeding, or expecting to conceive at any time during the study • Female and is expecting to donate eggs or male and is expecting to donate sperm during the study
Drugs	Intervention	Immediate switch group • Doravirine 100 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg as an STR once daily
	Comparator(s)	Delayed switch group One of the following dosing regimens once daily for the first 24 weeks: • baseline regimen of ritonavir- or cobicistat-boosted protease inhibitor (dosing as per patient's current treatment regimen) or • baseline regimen of cobicistat-boosted elvitegravir (dosing as per patient's current treatment regimen) or • baseline regimen of a non-nucleoside reverse transcriptase inhibitor (dosing as per patient's current treatment regimen) or • baseline regimen of two nucleoside reverse transcriptase inhibitors (dosing as per patient's current treatment regimen). For week 24 to 48 all patients were switched to doravirine 100 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg as an STR once daily
Duration	Run-in	4 weeks
	Treatment	48 weeks
	Extension (OL)	144 weeks
Outcomes	Primary end point(s)	Percentage of participants maintaining HIV-1 RNA < 50 copies/mL at week 48 for the ISG compared to week 24 for the DSG
	Other end points	• Change from baseline in fasting low-density lipoprotein cholesterol (LDL-C) (week 24) • Change from baseline in fasting non-high-density lipoprotein cholesterol (non-HDL-C) (week 24) • Percentage of participants maintaining HIV-1 RNA < 50 copies/mL (week 24) • Change from baseline in cluster of differentiation (CD4) cell counts (week 48/week 24, and week 24 only) • Percentage of participants maintaining HIV-1 RNA < 40 copies/mL (week 24) • Percentage of participants with HIV-1 RNA > = 50 copies/mL (week 48/week 24)
Notes	Publications	clinicaltrials.gov identification code : NCT02397096

ART = antiretroviral therapy; CD4 = cluster of differentiation 4; DSG = delayed switch group; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; RNA = ribonucleic acid; SRT = single-tablet regimen.

[a] Data were added or modified by the CADTH Common Drug Review reviewer based on data from the clinical study report.[8]

Intervention and Comparators

Approximately 660 patients will be stratified by the ART class used in their regimen at screening (an RTV-boosted PI, specifically atazanavir, darunavir (DRV), or lopinavir versus a COBI-boosted PI versus COBI-boosted EVG or an NNRTI, specifically, EFV, nevirapine, or rilpivirine [RPV]) and, for patients whose regimen at screening includes an RTV-boosted PI, by use of lipid-lowering therapy at study day 1. The four strata are RTV-boosted PI with lipid-lowering therapy at day 1, RTV-boosted PI without lipid-lowering therapy at day 1, COBI-boosted PI, and COBI-boosted EVG or an NNRTI. Patients will be randomized in a 2:1 ratio to an immediate switch to MK-1439A (DOR/3TC/TDF) on study day 1 (immediate switch group [ISG]) or delayed switch to MK-1439A at study week 24 (delayed switch group [DSG]). The DSG will continue their baseline regimen until the time of switch to MK-1439A

at study week 24. The total duration of treatment for a given patient who does not continue into study extension 1 is 48 weeks; for patients who continue into study extension 1, 144 weeks; and for patients who continue into study extension 2, a maximum of 240 weeks.

Outcomes

The protocol specified the primary efficacy end point as the proportion of patients with HIV-1 RNA of fewer than 50 copies per mL. The proportion of patients with HIV-1 RNA of fewer 40 copies per mL was a secondary end point. Note that the European Union considers the proportion of patients with HIV-1 RNA of fewer than 40 copies per mL at the primary time points (above) as the primary end point.

Note that the secondary efficacy hypothesis testing noninferiority between treatment groups at study week 24 is only supportive to the primary efficacy hypothesis and was not included in the multiplicity strategy in this study.

Statistical Analyses

The primary hypothesis will be assessed based on the proportion of patients maintaining HIV-1 RNA of fewer than 50 copies per mL by the Abbott RealTime HIV-1 assay at study week 48 in the ISG and at study week 24 in the DSG. The Non-Completer=Failure approach as defined by the FDA Snapshot approach will be used as the primary approach for handling missing data. All missing data will be treated as failures regardless of the reason.

The difference in proportions between treatment groups and the associated 95% CI will be calculated using the stratum-adjusted Mantel–Haenszel method with the difference weighted by the harmonic mean of the sample size per arm for each stratum. Only two strata will be used for this analysis: RTV-boosted or COBI-boosted PI versus COBI-boosted EVG or NNRTI as a component of the baseline regimen. The use of lipid-lowering therapy is not expected to be associated with virologic response; therefore, stratification by use of lipid-lowering therapy will not be included in the analyses of virologic response.

For the primary hypothesis, an immediate switch to MK-1439A on study day 1 will be concluded noninferior to continuation of the baseline regimen, if the lower bound of the two-sided 95% CI for the difference in the proportion of patients maintaining HIV-1 RNA of fewer than 50 copies per mL by the Abbott RealTime HIV-1 assay (ISG minus DSG) is greater than –8 percentage points. It can be further concluded that an immediate switch to MK-1439A is superior to continuation of the baseline regimen if the lower bound of the two-sided 95% CI for the difference in response rates (ISG minus DSG) is greater than zero contingent upon satisfying the multiplicity criteria. A similar approach will be used for the supportive secondary efficacy hypotheses for noninferiority and superiority at study week 24 for both treatment groups.

CDR reviewer comment: The following outcomes were tested in the given order as part of the statistical testing hierarchy; proportion of patients maintaining HIV-1 RNA of fewer than 50 copies per mL testing noninferiority at study week 48 for the ISG versus baseline regimen at study week 24 for the DSG, mean change from baseline in each treatment group for fasting LDL-C at week 24, mean change from baseline in each treatment group for fasting non-HDL-C at week 24, proportion of patients maintaining HIV-1 RNA of fewer than 50 copies per mL testing superiority at study week 48 for the ISG versus baseline regimen at study week 24 for the DSG.

B. Results

Baseline Characteristics

- In terms of demographics, there were marginally more females in the ISG versus the DSG.
- The majority of patients were on a PI class of medication at entry.

Table 7: Summary of Baseline Characteristics in DRIVE-SHIFT[a]

	DRIVE-SHIFT	
	ISG (N = 447)	**DSG (N = 223)**
Demographic and Clinical Characteristics		
Male, n (%)	372 (83.2)	194 (87.0)
Race n (%) White Black Asian	 344 (77.0) 56 (12.5) 17 (3.8)	 168 (75.3) 34 (15.2) 8 (3.6)
Age (years) Mean (SD)	 43.1 (10.1)	 43.7 (10.6)
Baseline CD4 Cell Count (cells/mm^3) Mean (SD)	 664.9 (295.3)	 649.9 (279.2)
Baseline Plasma HIV-1 RNA, n (%) < 50 copies/mL	 436 (97.5)	 222 (99.6)
History of AIDS, n (%) Yes	 80 (17.9)	 35 (15.7)
Baseline Hepatitis Status HBV and/or HCV positive HBV positive only HCV positive only HBV and HCV negative	 14 (3.1) 12 (2.7) 2 (0.4) 433 (96.9)	 9 (4.0) 7 (3.1) 2 (0.9) 214 (96.0)
ART History, n (%)		
Ritonavir-boosted PI ATV DRV LPV	312 (69.8) 96 (21.5) 161 (36.0) 54 (12.1)	155 (69.5) 43 (19.3) 81 (36.3) 31 (13.9)
Cobicistat-boosted PI DRV	5 (1.1)	1 (0 .4)
Cobicistat-boosted elvitegravir NNRTI EFV NVP RPV	25 (5.6) 106 (23.7) 78 (17.4) 17 (3.8) 11 (2.5)	12 (5.4) 55 (24.7) 36 (16.1) 12 (5.4) 7 (3 .1)
Duration of ART Regimen Prior to Enrolment (months), Mean (SD)	56.6 (38.4)	58.6 (37.0)

ART = antiretroviral therapy; ATV = atazanavir; CD4 = cluster of differentiation 4; DRV = darunavir; DSG = delayed switch group; EFV = efavirenz; HBV = hepatitis B virus; HCV = hepatitis C virus; ISG = immediate switch group; LPV = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RNA = ribonucleic acid; RPV = rilpivirine; SD = standard deviation.

[a] Table added by CADTH Common Drug Review Reviewer based on data from the DRIVE-SHIFT clinical study report.[8]

Patient Disposition

- Patients were randomized 2:1 (DOR/3TC/TDF versus current therapy).
- Intervention (DOR/3TC/TDF) is the ISG and the comparator arm (current therapy) is the DSG.
- There appears to be a small trend for higher AEs in the ISG versus DSG.

Table 8: Summary of Patient Disposition for DRIVE-SHIFT

Disposition	DOR/3TC/TDF	Comparator Arm
Screened, N	852	852
Randomized, N	447	223
Discontinued, N (%)	40 (8.9%)	21 (9.4%)
WDAEs, N (%)	13 (2.9%)	3 (1.3%)
Withdrawal due to SAEs, N (%)	0 (0%)	0 (0%)
Lost to follow-up, N (%)	5 (1.1%)	4 (1.8%)
Lack of efficacy, N (%)[a]	5 (1.1%)	2 (0.9%)
Withdrawal by patient, N (%)[a]	11 (2.4%)	3 (1.3%)
Other reason, N (%)[a]	6 (1.3%)	9 (4.0%)
Intention to treat, N	450	223
Full analysis set,[a] N	447	223
Per protocol, N	NA	NA
Safety, N	447	223

DOR/3TC/TDF = doravirine at 100 mg, lamivudine at 300 mg, and tenofovir disoproxil fumarate at 300 mg; NA = not applicable; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Data added or modified by the CADTH Common Drug Review reviewer based on data from the clinical study report.[8]

CDR reviewer comment: Full disposition details for DRIVE-SHIFT are included in the Pifeltro CDR Clinical Review Report.

Efficacy

For the primary efficacy end point, the proportion (%) of patients with HIV-1 RNA of fewer than 50 copies per mL by the FDA Snapshot approach was 90.8% (406 out of 447) for the ISG at study week 48 and 94.6% (211 out of 223) for the DSG at study week 24. The observed treatment difference (ISG minus DSG) was −3.8%, with an associated 95% CI of (−7.9% to 0.3%), demonstrating noninferiority given that the lower bound is greater than the predefined noninferiority bound of −8%. After demonstrating the superiority on fasting lipids (see Section 2.4), the superiority of efficacy was assessed. The superiority of efficacy was not established given that the lower bound of the 95% CI is below zero. The analysis of the proportion of patients with HIV-1 RNA of less than 40 copies per mL by FDA Snapshot approach showed similar results as the primary analysis.

The analysis of the proportion of patients with HIV-1 RNA of fewer than 50 copies per mL by the observed failure approach showed the observed treatment difference (ISG minus DSG) was 0.2%, with an associated 95% CI of (–2.2 to 2.6). The analysis of the proportion of patients with HIV-1 RNA of fewer than 40 copies per mL by the observed failure approach showed similar results.

CDR reviewer comment: Additional efficacy outcomes are summarized in the Pifeltro Clinical Review Report.

DRIVE-FORWARD (PN-018)

CDR reviewer comment: The DRIVE-FORWARD study is considered supporting data and is not a pivotal trial for DOR/3TC/TDF because the DOR intervention group were administered NRTI backbone therapies that were not consistent with the Delstrigo product. Thus, the information included in this section has not been reviewed or appraised by CDR. A thorough review of this trial may be found in the CDR Clinical Review Report for Pifeltro.

A. Study Characteristics

A phase III, multi-centre, double-blind, randomized, active comparator-controlled clinical trial to evaluate the safety and efficacy of DOR (MK-1439) 100 mg once daily versus DRV 800 mg once daily plus RTV 100 mg once daily, each in combination with Truvada or Epzicom/Kivexa, in patients with treatment-naive HIV-1 infection.

Table 9: Details of DRIVE-FORWARD[a]

Characteristics		DRIVE-FORWARD
Study Design	Objective	Pivotal efficacy and safety study
	Blinding	Double blind
	Study period	2014-12 to 2016-09
	Study centres	Argentina (4), Australia (6), Austria (4), Canada (5), Chile (5), Denmark (3), France (8), Germany (12), Italy (1), Puerto Rico (4), Romania (6), Russia (11), South Africa (3), Spain (10), UK (11), US (40)
	Design	Noninferiority
Study Population	Randomized (N)	769
	Inclusion criteria	• Is HIV-1 positive and has HIV treatment indicated based on physician assessment • Has received no (0 days of) antiretroviral therapy, including investigational antiretroviral agents • Is considered clinically stable with no signs or symptoms of active infection for at least two weeks prior to the start of treatment • Female is highly unlikely to become pregnant, or male is highly unlikely to impregnate a partner because they are not of reproductive potential, or agree to practice abstinence or use acceptable contraception for up to 14 days after the last dose of study drug
	Exclusion criteria	• Uses or has had a recent history of using recreational or illicit drugs • Has been treated for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1 • Has documented or known resistance to study drugs including doravirine, darunavir, ritonavir, emtricitabine, tenofovir, abacavir, and/or lamivudine • Has participated in a study with an investigational compound/device within the prior month, or anticipates doing so during this study • Has used systemic immunosuppressive therapy or immune modulators within the prior 30 days, or anticipates doing so during this study • Has significant hypersensitivity or other contraindication to any of the components of the study drugs • Has a current (active) diagnosis of acute hepatitis due to any cause • Is pregnant, breastfeeding, or expecting to conceive at any time during the study • Female who expects to donate eggs, or male who expects to donate sperm at any time during the study
Drugs	Intervention	DOR (100 mg) one tablet orally once daily in combination with either TDF 300 mg/FTC 200 mg FDC or ABC 600 mg/3TC 300 mg FDC one tablet orally once a day

Characteristics		DRIVE-FORWARD
	Comparator(s)	DRV 800 mg with RTV 100 mg orally once daily in combination with either TDF 300 mg/FTC 200 mg FDC or ABC 600 mg/3TC 300 mg FDC one tablet orally once a day
Duration	Run-in	6.5 weeks
	Treatment	96 weeks
	Extension (OL)	96 weeks
Outcomes	Primary end point(s)	Proportion of participants with HIV-1 RNA < 50 copies/mL at week 48
	Other end points	Proportion of participants with HIV-1 RNA < 50 copies/mL at week 96 Change from baseline in CD4 T-cell count at week 48 and 96 Proportion of participants with HIV-1 RNA < 40 copies/mL at week 48 and 96
Notes	Publications	clinicaltrials.gov identification code: NCT02275780, Molina et al.[11]

3TC = lamivudine; ABC = abacavir; CD4 = cluster of differentiation 4; DOR = doravirine; DRV = darunavir; FDC = fixed-dose combination; FTC = emtricitabine; OL = open label; RNA = ribonucleic acid; RTV = ritonavir; TDF = tenofovir disoproxil fumarate.

[a] Data were modified by the CADTH Common Drug Review reviewer based on data from the clinical study report.[12,13]

Intervention and Comparators

Seven hundred and sixty-nine patients were stratified by screening HIV-1 RNA (≤ or > 100,000 copies per mL) and NRTI backbone therapy (Truvada or Epzicom/Kivexa, as selected by the investigator), and randomized within strata in a 1:1 ratio to receive either MK-1439 100 mg once daily with placebo DRV/RTV or DRV/RTV (800 mg/100 mg once daily) with placebo MK-1439, each in combination with the selected backbone therapy. The duration of treatment for a given patient in the base study is 96 weeks (approximately two years). The primary end point is the proportion of patients achieving HIV-1 RNA of fewer than 50 copies per mL at week 48.

Outcomes

The primary efficacy end point was the proportion of participants who had plasma HIV-1 RNA of fewer than 50 copies per mL at week 48 as defined by the FDA Snapshot algorithm. Secondary end points were HIV-1 RNA of fewer than 40 copies per mL and change from baseline in CD4 T-cell count. Exploratory end points were HIV-1 RNA of fewer than 200 copies per mL, time to loss of virological response, PDVF, and the development of viral resistance to the study medications. Safety outcomes were change from baseline in LDL-C and non-HDL-C, incidence of AEs, time to discontinuation because of AEs, and predefined limits of change in laboratory parameters.

Statistical Analyses

Assuming a true response rate of 80% at week 48, a sample size of 340 participants per treatment group would achieve 90% power to detect noninferiority at a one-sided alpha of 0.025. Noninferiority was established if the lower bound of the two-sided 95% CI for the treatment difference (DOR minus DRV) was greater than −10 percentage points. The efficacy analyses used the FAS, defined as all randomly assigned participants who received at least one dose of study treatment with participants included in the treatment group to which they were randomly assigned. Assessment of the primary efficacy end point used the FDA Snapshot approach, which treats all missing data as treatment failures regardless of the reason, including early discontinuation of study therapy. Participants who changed

background NRTI therapy after week 2 with HIV-1 RNA of 50 copies per mL or higher at the time of switch were counted as treatment failures at subsequent visits. The difference between treatment groups in the proportion of participants achieving HIV-1 RNA of fewer than 50 copies per mL and the associated 95% CIs were calculated by the stratum-adjusted Mantel–Haenszel method with the difference weighted by the harmonic mean of the sample size per arm for each stratum. The secondary and exploratory virological end points were analyzed using the same method as the primary end point. SAS software (version 9.3 or 9.4; SAS Institute, Cary, NC, USA) was used for all analyses.

B. Results

Baseline Characteristics

Table 10: Baseline Characteristics of DRIVE-FORWARD

	Doravirine Regimen (n = 383)	Darunavir and Ritonavir Regimen (n = 383)
Sex		
Men	319 (83%)	326 (85%)
Women	64 (17%)	57 (15%)
Race		
White	280 (73%)	280 (73%)
Black	86 (22%)	88 (23%)
Asian	7 (2%)	7 (2%)
Other	10 (3%)	7 (2%)
Ethnic origin		
Hispanic or Latino	93 (24%)	86 (22%)
Region		
Europe	170 (44%)	179 (47%)
North America	140 (37%)	146 (38%)
South America	38 (10%)	33 (9%)
Africa	23 (6%)	22 (6%)
Asia-Pacific	12 (3%)	3 (1%)
Median age, years	33.0 (27 to 41)	34.0 (27 to 43)
Median CD4 count (cells per µL)	410 (299 to 550)	393 (257 to 547)
CD4 Count (cells per µL)		
≤ 200	42 (11%)	67 (17%)
> 200	341 (89%)	316 (83%)
Median HIV-1 RNA $\log_{10}$ copies per mL	4.4 (4.0 to 4.9)	4.4 (4.0 to 4.8)
HIV-1 RNA Concentration		
≤ 100 000 copies per mL	300 (78%)	308 (80%)
> 100 000 copies per mL	83 (22%)	74 (19%)
Previous AIDS diagnosis	36 (9%)	37 (10%)
NRTI Component		
Tenofovir and emtricitabine	333 (87%)	335 (87%)
Abacavir and lamivudine	50 (13%)	48 (13%)
Hepatitis B or C positive	11 (3%)	18 (5%)
HIV Viral Subtype		

	Doravirine Regimen (n = 383)	Darunavir and Ritonavir Regimen (n = 383)
Subtype B	266 (69%)	272 (71%)
Subtype non-B	117 (31%)	111 (29%)

CD4 = cluster of differentiation 4; NRTI = nucleoside reverse transcriptase inhibitor; RNA = ribonucleic acid.

Patient Disposition

Table 11: Summary of Patient Disposition for DRIVE-FORWARD

Disposition	Doravirine	Ritonavir-Boosted Darunavir
Screened, N	1,027	1,027
Randomized, N	769	769
Discontinued, N (%)	56 (14.6%)	71 (18.5%)
WDAEs, N (%)	4 (1.0%)	12 (3.1%)
Withdrawal due to SAEs, N (%)	0 (0%)	0 (0%)
Lost to follow-up, N (%)	17 (4.4%)	19 (4.9%)
Intention to treat, N	385	384
Per protocol, N	NA	NA
Safety, N	385	384

NA = not applicable; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Efficacy

At week 48, 321 (84%) of 383 participants in the DOR group and 306 (80%) of 383 participants in the DRV group had plasma HIV-1 RNA of fewer than 50 copies per mL (difference, 3.9%; 95% CI, –1.6 to 9.4; see Table 12), showing noninferiority of DOR to DRV. Similar results were obtained in the per-protocol analysis. The full characterization of virological outcomes at week 48 defined by the FDA Snapshot algorithm was similar between the treatment groups. The proportion of participants with HIV-1 RNA of fewer than 50 copies per mL at each time point was similar between the treatment groups, with both groups reaching a plateau at week 24. Among the participants with HIV-1 RNA of 100,000 copies per mL or higher at baseline, 64 (81%) of 79 participants in the DOR group and 55 (76%) of 72 participants in the DRV group had plasma HIV-1 RNA of fewer than 50 copies per mL at week 48 (difference, 3.0%; 95% CI, –11.2 to 17.1. In the small subgroup of participants with HIV-1 RNA of more than 500,000 copies per mL at baseline, 14 (82%) of 17 participants in the DOR group and six (50%) of 12 participants in the DRV group had plasma HIV-1 RNA of fewer than 50 copies per mL at week 48 (difference 30.9%; 95% CI, –4.1 to 65.9). Among participants with low CD4 count (< 200 cells per µL) at baseline, 34 (83%) of 41 in the DOR group and 44 (72%) of 61 in the DRV group had HIV-1 RNA of fewer than 50 copies per mL at week 48 (difference, 9.4%; 95% CI, –7.4 to 26.2).

Results for the secondary virological end points were consistent with those for the primary end point. Using the observed failure approach, at week 48, 321 (88%) of 364 participants in the DOR group and 306 (86%) of 355 participants in the DRV group achieved HIV-1 RNA of fewer than 50 copies per mL. At week 48, the mean change from baseline in CD4 cell counts was 193 per µL (95% CI, 172 to 214) in the DOR group and 186 per µL (95% CI, 168 to 204) in the DRV group (mean difference, 7.1 per µL; 95% CI, –20.8 to 35.0).

Table 12: Efficacy Results for DRIVE-FORWARD (Week 48)

	Doravirine regimen (n=383)	Darunavir and ritonavir regimen (n=383)
HIV-1 RNA <50 copies per mL	321 (84%)	306 (80%)
HIV-1 RNA ≥50 copies per mL	43 (11%)	50 (13%)
HIV-1 RNA ≥50 copies per mL in week 48 window	12 (3%)	14 (4%)
Changed background therapy	0	1 (<1%)
Treatment discontinued before week 48 due to lack of efficacy	8 (2%)	11 (3%)
Treatment discontinued before week 48 for other reasons with last available HIV-1 RNA ≥50 copies per mL	23 (6%)	24 (6%)
No virological data available in the week 48 window	19 (5%)	27 (7%)
Discontinued study because of adverse event or death*	5 (1%)	11 (3%)
Discontinued study for other reasons†	11 (3%)	15 (4%)
On study but missing data in the week 48 window	3 (1%)	1 (<1%)

Data are n (%). Doravirine and ritonavir-boosted darunavir regimens were given with fixed-dose combinations of tenofovir and emtricitabine or abacavir and lamivudine. *Participants who discontinued treatment because of adverse event or death at any timepoint between day 1 and the end of the week 48 window if this resulted in no virological data on treatment during the specified window. †Other reasons include loss to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol violation, and participant decision.

Table 2: **Virological outcomes at week 48 window (days 295–378)**

RNA = ribonucleic acid.

2.2 Critical Appraisal of Pivotal Clinical Studies

The following section provides an overall appraisal of the evidence pertaining to the two relevant studies. This review was conducted in tandem with the evaluation of the DOR single-dose product (Pifeltro), which includes additional study data that are not presented in this report. Readers are therefore suggested to consult the Pifeltro report for additional context.

2.2.1 Internal Validity

Both DRIVE-AHEAD and DRIVE-SHIFT were randomized studies that appear to have used acceptable methods interactive voice/web response system (IVRS/IWRS), computer-generated allocation schedule) to randomize patients to treatment groups. The double-blind trial, DRIVE-AHEAD, performed necessary measures to maintain blinding and conceal treatment allocation; all study medications including respective placebos, were packaged and supplied in identical containers and/or bottles. The clinical expert consulted for this review indicated that EFV is associated with an increased incidence of neuropsychiatric AEs; a statement consistent with the relatively higher frequency of dizziness and sleep disorders and disturbances reported among patients receiving EFV/FTC/TDF in DRIVE-AHEAD. It is possible for patients to surmise the greater potential for neuropsychiatric side effects with EFV/FTC/TDF administration, which might compromise treatment blinding. Many efficacy and safety outcomes were measured in blood and plasma samples in an

objective manner; therefore, reporting bias, if any unblinding occurred, was less likely. However, the possibility remains for ascertainment of treatment allocation to influence patient reporting of subjective outcomes (e.g., neuropsychiatric AEs), as well as influence patients' decisions whether to remain in the trial, thus potentially biasing the primary efficacy outcome (given that patients who discontinued the study were considered to have failed to achieve the primary outcome).

The primary efficacy end point in both studies was the proportional differences in HIV-1 RNA of fewer than 50 copies per mL between the treatment groups. While this is the FDA-recommended efficacy outcome for treatment-naive patients, the end point of interest in switch trials is the proportional difference in HIV-1 RNA of 50 copies per mL or more (not success of fewer than 50 copies per mL as per the manufacturer's analysis).[9] This is because switch trials include patients who are already virologically suppressed; therefore, the end point should be focused on patients who lose virologic control post-switching. Even though the proportional difference in HIV-1 RNA of 50 copies per mL or more was measured in DRIVE-SHIFT, this was not part of the statistical testing hierarchy and not compared against a pre-specified noninferiority margin. Therefore, the primary efficacy outcome in DRIVE-SHIFT is inconsistent with FDA recommendations for switch trials. Notably, the manufacturer of DRIVE-SHIFT indicated that the latest issue of FDA guidance for industries with these updated recommendations was published after the trial began.

For both trials, it is unclear if all of the patients were classified appropriately according to the FDA Snapshot algorithm for the outcome of HIV-1 RNA of 50 copies per mL of greater, given that patients lacking virologic data were not included as failures (assumption of HIV-1 RNA of 50 copies per mL or greater). The impact this would have had on the results in uncertain. Other secondary efficacy outcomes, as well as safety end points, were consistent with FDA guidance and commonly measured in HIV trials. One trial (DRIVE-SHIFT) assessed an HRQoL outcome relevant for this review; however, only an assessment of the EuroQol 5-Dimensions 5-Levels Visual Analogue Scale (EQ-5D-5L VAS) questionnaire was done without generating an index score; which had no supporting evidence for the validity and minimally clinically important difference among HIV patients from the literature.

The statistical analyses plan, including missing data handling for the primary outcome (i.e., missing data = failure and missing data = excluded), deriving sample size and power, and adjusting for multiple comparisons were done appropriately and generally followed the FDA guidance for HIV trials. One notable exception was the handling of missing data in DRIVE-SHIFT. After the initial database lock (dated March 27, 2018) the manufacturer identified a number of patients with missing HIV-1 RNA data at key efficacy time points, all of whom were in the ISG group. According to the FDA Snapshot approach, these patients would be counted as treatment failures. The manufacturer discovered additional blood samples were available from the pharmacokinetic and viral resistance samples that could be used to test for HIV-1 RNA (week 24, n = 3; week 48, n = 2). With the addition of sample data for these five patients, the noninferiority margin was met for the primary outcome; however, noninferiority was not met based on the data from the initial database lock.

The studies did not use a true intention-to-treat population as several patients were excluded after randomization; however, the numbers are low and are unlikely to affect the study results. Moreover, the double-blind trial, but not the switch trial, appropriately performed the primary efficacy analysis in a per-protocol population with findings supportive of analysis using the FAS population.

The treatment groups appeared to be generally balanced with respect to baseline characteristics within studies. The exception to this is a higher proportion of patients in the ISG group with immune system disorders, drug hypersensitivity, neoplasms, and psychiatric disorders in DRIVE-SHIFT. Although these differences may have arisen from chance, it is possible that randomization may also have failed. The frequency of dropouts was high, particularly among treatment-naive patients in DRIVE-AHEAD (ranged from 13% to 17% by week 48 and between 18% and 24% by week 96). Notably, patients receiving DOR in this trial had fewer dropouts, in part due to fewer AEs. The higher incidences of dropouts in the comparator groups may bias the results in favour of DOR as dropouts were treated as treatment failures.

In the switch study, the primary efficacy analyses, as well as a number of secondary efficacy and safety analyses, involved comparing the ISG group at week 48 with the baseline regimen of the DSG group at week 24. This form of differential follow-up between groups is unusual and the CDR review team is uncertain of the impact this has on the results; however, between-treatment comparisons based on the same duration of follow-up would have more internal validity. While comparisons for efficacy end points were also reported between the treatment groups at week 24, those were not controlled for multiplicity. The FDA guidance document[9] indicates virologic response at 48 weeks to be the recommended time point for comparative efficacy determination among patients who are treatment naive or had previous treatment with a well-documented treatment history demonstrating no virologic failure. The guidance states, “Twenty-four weeks of data is appropriate for drugs that have some benefit over existing options (e.g., better efficacy, tolerability, ease of administration), while 48 weeks is recommended for drugs with comparable characteristics to existing options.” The expert consulted for this CDR review, however, indicated that 24 weeks is a reasonable follow-up period for viral breakthrough after treatment switch, but that a longer duration of observation may increase the number of AEs identified.

2.2.2 External Validity

Both DRIVE-AHEAD and DRIVE-SHIFT were multinational trials, enrolling patients from a range of countries across North America, Central America, South America, Western Europe, and Asia. Approximately 20% to 25% of the screened patients did not meet the eligibility criteria, primarily due to resistance to any of the study medications (both trials) and having plasma HIV-1 RNA level of fewer than 1,000 copies per mL at screening (DRIVE-AHEAD only). According to the clinical expert consulted for this review, it is standard of care (SOC) to have baseline resistance tested to prevent prescription of an inadequately active ARV; thus, exclusion of patients based on resistance testing does not affect the generalizability of the reviewed trials. Other notable eligibility criteria included not having serious liver or kidney impairments (i.e., not having exclusionary laboratory values), active infection, and acute hepatitis. Therefore, the results may not be generalized to patients with these conditions. A small proportion of patients (less than 5%) were hepatitis B virus and/or hepatitis C virus positive; however, the clinical expert consulted by CDR indicated that hepatitis coinfection should not negatively affect the bioavailability of the ARVs or their effectiveness.

The clinical expert consulted for this review indicated that the baseline demographic and clinical characteristics in DRIVE-AHEAD were generally reflective of treatment-naive patients in the Canadian setting. It was, however, noted that the number of patients with a history of AIDS was higher than expected for a treatment-naive population (range: 12% to 15% across groups). The clinical expert consulted by CDR indicated that AIDS is associated with lower CD4 counts and higher viral loads, which may lead to a lower likelihood of

virologic success. A higher percentage of patients in the switch trial had a history of AIDS compared with the treatment-naive patients, likely resulting from their longer history of living with HIV-1 infection than newly diagnosed treatment-naive patients.

The comparator used in DRIVE-AHEAD (EFV/FTC/TDF) is infrequently prescribed in contemporary clinical practice according to the expert, and has been largely displaced by first-line therapies, which are better tolerated regimens endorsed by the US Department of Health and Human Services (DHHS) guidelines,[4] e.g., bictegravir (BIC)/tenofovir alafenamide (TAF)/FTC (Biktarvy), EVG/c/TAF/FTC (Genvoya), and dolutegravir (DTG)/ abacavir (ABC)/3TC (Triumeq). EFV is known to cause neuropsychiatric adverse effects, which should be considered when assessing the generalizability of the safety data.

2.3 Summary of Safety

2.3.1 Safety Evaluation Plan[21]

DOR (also known as MK-1439) is an NNRTI being developed by the applicant as a once-daily oral treatment for HIV-1 infection in antiretroviral, treatment-naive adults aged 18 years and older. It is being developed as both the single-agent DOR (100 mg) and as an FDC with 3TC (300 mg) and TDF (300 mg) (also known as MK-1439A, but hereafter referred to as DOR/3TC/TDF). DOR (in combination with other antiretroviral medicinal products) and DOR/3TC/TDF are being developed in a hybrid clinical development program that includes mutually supportive phase II and phase III trials of the DOR single entity and DOR/3TC/TDF. The trials supporting this application and contributing data to this summary of clinical safety include 36 phase I trials, one phase IIb dose-ranging trial (Protocol 007 [P007]), and two phase III trials (P018 and P021).

CDR reviewer comment: The manufacturer refers to a number of phase I, II, and III trials with regard to the safety evaluation for DOR. However, the CDR reviewers limited the comparative safety evaluation of DOR/3TC/TDF in the two aforementioned phase III trials, DRIVE-AHEAD and DRIVE-SHIFT.

2.3.2 Safety Populations Evaluated[21, 22]

Most (n = 650) of the 678 patients who received DOR or DOR/3TC/TDF in the phase I trials were healthy adult patients with no secondary diagnoses. P019 included a cohort of eight patients with moderate hepatic insufficiency (a score of 7 to 9 on the Child-Pugh scale), and P051 included a cohort of eight patients with severe renal insufficiency (estimated glomerular filtration rate of less than 30 L/min/1.73 m^2). Twelve patients in P005 were treatment-naive HIV-1 infected subjects. Overall, the percentage of male and female patients was 62.1% and 37.9%, respectively. The mean age was 39.5 years (range: 19 to 78 years). The largest percentage of patients was white (62.9%) followed by black or African-American (29.6%), Asian (3.7%), and multiracial (3.1%).

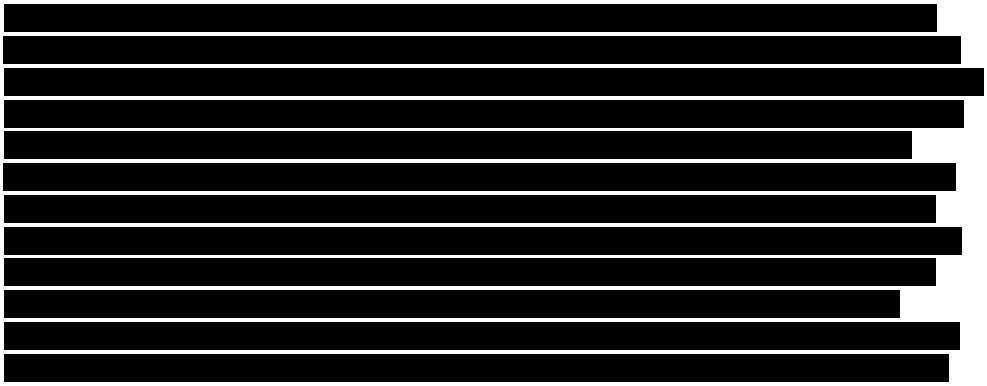
In the phase II and phase III clinical trials of PN-018 (DRIVE-FORWARD), PN-021 (DRIVE-AHEAD), and PN-024 (DRIVE-SHIFT), the percentage of male and female patients was 85.2% and 14.8%, respectively. The mean age was 36.8 years, most of the patients were aged 18 to 64 (range: 18 to 71). The largest percentage of patients was white (66.9%) followed by black or African-American (18.2%), Asian (7.1%), multiracial (6.3%), American Indian or Alaska Native (1.2%), and Native Hawaiian or other Pacific Islander (0.2%).

2.3.3 Overview of Safety[21,22]

In the phase I trials, DOR and DOR/3TC/TDF, given as single or multiple doses, alone or co-administered with other therapies, were generally well tolerated with no safety issues identified. No deaths occurred. A total of 202 (28.9%) patients reported at least one AE that was considered drug-related by the investigator. The most commonly reported drug-related AEs following administration of DOR, DOR/3TC/TDF, and DOR plus other trial drugs were headache (8.7%) and somnolence (5.0%). Following administration of placebo, the most common drug-related AE was headache (13.3%).

By week 96 in Protocol 007, the observed proportion of patients with drug-related AEs was lower in the DOR combined-treatment group (41.4%) compared with the EFV treatment group (58.3%); the lowest proportion of patients with drug-related AEs was observed in the DOR 100 mg treatment group (35.2%). Overall, the most commonly reported drug-related AEs for DOR were dizziness, abnormal dreams, and nightmare, but they were consistently lower for the DOR combined-treatment group compared with the EFV treatment group, especially dizziness (DOR combined, 5.6%, versus EFV, 26.9%) and abnormal dreams (DOR combined, 9.1%, versus EFV, 14.8%). AEs that were considered by the investigator to be drug-related and moderate or severe in intensity were experienced by fewer patients in the DOR combined-treatment group (13.8%) compared with the EFV treatment group (30.6%). The most common drug-related AE by week 96 (incidence of 2% or greater) that was considered by the investigator to be moderate or severe in intensity for the DOR treatment group was insomnia. No deaths occurred.

In DRIVE-FORWARD, drug-related AEs were reported with a similar proportion by patients in the DOR treatment group (30.5%) compared with the DRV+r treatment group (32.1%). Drug-related AEs were most frequently associated with the SOC of gastrointestinal disorders with a lower observed proportion in the DOR treatment group compared with the DRV+r treatment group. Overall, the most frequently (incidence more than 2% in one or more of the treatment groups) reported drug-related AEs were diarrhea, nausea headache, fatigue, dizziness, and upper abdominal pain. Similar to the analysis of all AEs, drug-related diarrhea was reported for fewer patients in the DOR group (5.5%) compared with the DVR+r group (12.8%). No other clinically relevant differences between treatment groups were observed. The proportions of patients with AEs that were considered by the investigator to be drug related and moderate or severe in intensity were similar in both treatment groups (DOR, 6.5%, versus DRV+r, 7.0%). The most commonly reported drug-related AE of moderate or severe intensity by week 48 (incidence higher than 0%) was diarrhea (DOR 1.6% versus DRV+r 1.8%).



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In DRIVE-AHEAD, drug-related AEs were reported for a lower proportion of patients in the DOR/3TC/TDF treatment group (31.0%) compared with the EFV/FTC/TDF treatment group (62.9%). Drug-related AEs were most frequently associated with the SOC of nervous system disorders. A lower proportion of patients in the DOR/3TC/TDF treatment group (12.9%) compared with the EFV/FTC/TDF treatment group (37.9%) experienced drug-related AEs in this SOC. The most commonly reported drug-related AEs (2% or more of patients in either treatment group presented in descending order of DOR frequency) were dizziness, somnolence, headache, abnormal dreams, and rash. Notably, the AE of dizziness was disproportionally higher in the EFV/FTC/TDF group (31.9%) compared with the DOR/3TC/TDF group (6.6%). Rash was also reported at a higher rate for the EFV/FTC/TDF group (8.5%) compared with the DOR/3TC/TDF group (1.6%). The other reported drug-related AEs did not have meaningful clinical differences between treatment groups. AEs considered by the investigator to be drug-related and moderate or severe in intensity were experienced by fewer patients in the DOR/3TC/TDF treatment group (10.4%) compared with the EFV/FTC/TDF treatment group (25.0%).

[redacted]

[redacted]

In DRIVE-SHIFT:

ISG study weeks 0 to 24 (DOR/3TC/TDF), DSG study weeks 0 to 24 (baseline regimen): During the first 24 weeks of the trial, AEs and drug-related AEs were reported for a higher proportion of participants in the ISG (DOR/3TC/TDF) than in the DSG (baseline regimen). AEs for the majority of participants in both groups were of mild-to moderate intensity and the majority of the AEs were considered by the investigator to be unrelated to the study medication. The incidences of serious adverse events (SAEs), drug-related SAEs, and discontinuation due to AE were low (lower than 4%) and occurred with similar frequency in both groups.

ISG study weeks 0 to 24 (DOR/3TC/TDF), DSG study weeks 24 to 48 (DOR/3TC/TDF): The safety profiles of participants in the ISG and DSG were generally similar following their switch to DOR/3TC/TDF, regardless of whether the switch was immediate (ISG: study weeks 0 to 24) or delayed (DSG: study weeks 24 to 48).

DSG study weeks 0 to 24 (baseline regimen), DSG study weeks 24 to 48 (DOR/3TC/TDF): AEs and drug-related AEs were reported for a higher proportion of participants in the DSG during study weeks 24 to 48 (i.e., after switching to DOR/3TC/TDF) compared with study weeks 0 to 24 while on their baseline regimen. The proportion of participants in the DSG with AEs leading to discontinuation was low (less than 2%) both from weeks 0 to 24 (baseline regimen) and from weeks 24 to 48 (DOR/3TC/TDF). Additionally, the proportion of participants with SAEs was low (less than 4%) during both periods. The majority of the AEs were of mild-to-moderate intensity, and were considered by the investigator to be unrelated to the study medication.

Overall DOR/3TC/TDF: ISG study weeks 0 to 48 plus DSG study weeks 24 to 48: Of the 656 participants treated with DOR/3TC/TDF during the base study (ISG study weeks 0 to 48 plus DSG study weeks 24 to 48), 73.9% reported AEs and 19.7% reported drug-related AEs. The majority of the AEs were of mild-to-moderate intensity and were considered by the investigator to be unrelated to the study medication. Serious AEs were reported for few (less than 4%) participants, and few (less than 3%) participants discontinued due to an AE. No randomized participant died during the base study. One participant died during the screening period, and two participants died after discontinuation of the study drug.

ISG study weeks 0 to 24 (DOR/3TC/TDF), DSG study weeks 0 to 24 (baseline regimen): During the first 24 weeks of the trial, nasopharyngitis and headache were the only AEs reported for 5% or more of participants in either group. The proportion of participants with an AE of headache was higher in the ISG (DOR/3TC/TDF) than in the DSG (baseline regimen) during study weeks 0 to 24.

ISG study weeks 0 to 24 (DOR/3TC/TDF), DSG study weeks 24 to 48 (DOR/3TC/TDF): The AE profile for the DSG following the switch to DOR/3TC/TDF was comparable to that observed for the ISG during the first 24 weeks of the study (24 weeks of treatment with DOR/3TC/TDF for both groups). Overall, there were no clinically meaningful differences between treatment groups during the first 24 weeks of treatment with DOR/3TC/TDF (ISG: weeks 0 to 24; DSG: weeks 24 to 48).

DSG study weeks 0 to 24 (baseline regimen), DSG study weeks 24 to 48 (DOR/3TC/TDF): Following their switch to DOR/3TC/TDF, the only AE reported for 5% or more of participants in the DSG was headache.

Overall DOR/3TC/TDF: ISG study weeks 0 to 48 plus DSG study weeks 24 to 48: From weeks 0 to 48, the most frequently reported AEs for participants who received DOR/3TC/TDF were nasopharyngitis, headache, and diarrhea.

A summary of AEs with incidence greater than 0% during the base study (study weeks 0 to 48) is provided in Table 14.3-5 in the manufacturer-submitted CSR.[22] No AEs were reported for participants during the screening period [Table 14.3-10 in the manufacturer-submitted CSR[22]]. A listing by treatment group and participant of all AEs, including day of onset, intensity, and outcome is found in 16.2.7 in the manufacturer-submitted CSR.[22]

Study extension (post week 48): Summaries of AEs with incidences of 5% or greater and greater than 0% reported during the study extension are similar to those presented for the study week 48 analysis, respectively. Tables specifically designed for disclosure of clinical trial results in publicly accessible databases, displaying summaries of all SAEs with an incidence greater than 5% in either treatment group, and non-serious AEs with an incidence greater than 5%, can be found in 16.2.7.3.1, 16.2.7.3.2 in the manufacturer-submitted CSR,[22] respectively.

CDR reviewer comment: In the overview of safety section, the manufacturer refers to numerous tables in other documents rather than providing the applicable data here. For additional safety data the reader may refer to the Pifeltro CDR Clinical Review Report.

2.4 Bioequivalence

Please note that Merck conducted a comparative bioavailability trial (PN-026). However, Merck did not conduct a formal bioequivalence trial, since clinical efficacy and safety data are available for the DOR/3TC/TDF FDC. This data has been included in this submission as part of the clinical data, specifically results from DRIVE-AHEAD (PN-021) and DRIVE-SHIFT (PN-024).

Data for 3TC and TDF as it relates to area under the curve (AUC), maximum concentration (C_{max}), and time of peak concentration (T_{max}) is available in the DOR/3TC/TDF product monograph. However, as no bioequivalence trial was conducted, the data were taken from the product monographs of each respective product. As such, the following table has not been completed.

Table 13: Bioequivalence Profile for Combination Product*†

Parameter	Component A as Combination AB	Component A as A + B‡	Component B as Combination AB	Component B as A + B‡
$AUC_{(0-T)}$ • Mean • Standard deviation • Coefficient of variance • Ratio of relative means • 90% confidence interval				
C_{max} • Mean • Standard deviation • Coefficient of variance • Ratio of relative means • 90% confidence interval				
T_{max} • Mean • Standard deviation • Coefficient of variance				

$AUC_{(0-T)}$ = time-averaged area under the curve; C_{max} = maximum concentration; T_{max} = time of peak concentration.

*Add columns to the table, as needed, to accommodate the number of components.

†In accordance with current Health Canada bioequivalence standards and data requirements.

‡Component A plus Component B, given concurrently.

CDR reviewer comment: CDR agrees that given the availability of clinical trials comparing the Delstrigo STRs with other ARV regimens for the treatment of HIV-1, bioequivalence data comparing the STRs with its components is not critical to this review.

3. Pharmacoeconomic Evaluation

3.1 Manufacturer-Submitted Cost Information

Table 14: Cost Comparison of New Combination Product and Individual Components

Drug/Comparator	Strength	Dosage Form	Price	Recommended Daily Use	Daily Drug Cost
Doravirine/lamivudine/ tenofovir disoproxil fumarate (Delstrigo)	DOR 100 mg/ 3TC 300 mg/ TDF 300 mg	Tablet	$28.7900	One tablet daily	$28.7900
Doravirine (Pifeltro)	100 mg	Tablet	$16.6500	One tablet daily	$16.6500
Lamivudine (3TC and generics)	300 mg	Tablet	$7.2538	One tablet daily	$7.2538
Tenofovir disoproxil fumarate (Viread and generics)	300 mg	Tablet	$4.8884	One tablet daily	$4.8884
Total					$28.7922

3TC = lamivudine; DOR = doravirine; TDF = tenofovir disoproxil fumarate.

Note: Prices sourced from Ontario Drug Benefit e-Formulary, accessed October 22, 2018.

As noted previously, exclusivity for Delstrigo is based on the doravirine compound patent, CA 2794377, which expires March 2031. The other components, 3TC and TDF, are already generic.

The combination product of DOR/3TC/TDF at its list price of $28.7900 per tablet per day saves $0.0022 per day versus the individual components. Exclusive of markup and dispensing fee, this is a savings of $0.8000 per year in Ontario. Delstrigo offers the convenience of an STR without a premium on the cost of the individual components.

3.2 Cost Comparison Table

Table 15: Cost Comparison Table

Drug/Comparator	Strength	Dosage Form	Price	Recommended Daily Use	Average Daily Drug Cost
DOR/3TC/FTC	DOR 100 mg/ 3TC 300 mg/ TDF 300 mg	One tablet	Delstrigo ($28.7900)	One tablet daily	$28.7900
DTG/ABC/3TC	DTG 50 mg/ ABC 600 mg/ 3TC 300 mg	One tablet	Triumeq ($43.2020)	One tablet daily	$43.2020
EFV/TDF/FTC	EFV 600 mg/ TDF 300 mg/ FTC 200 mg	One tablet	Atripla and generics ($22.6600)	One tablet daily	$22.6600
EVG/COBI/TAF/FTC	EVG 150 mg/ c 150 mg/ TAF 10 mg/ FTC 200 mg	One tablet	Genvoya ($45.1440)	One tablet daily	$45.1440
EVG/COBI/TDF/FTC	EVG 150 mg/ c 150 mg/ TDF 300 mg/ FTC 200 mg	One tablet	Stribild ($48.0177)	One tablet daily	$48.0177

Drug/Comparator	Strength	Dosage Form	Price	Recommended Daily Use	Average Daily Drug Cost
RPV/TAF/FTC	RPV 25 mg/ TAF 25 mg/ FTC 200 mg	One tablet	Odefsey ($42.3670)	One tablet daily	$42.3670
RPV/TDF/FTC	RPV 25 mg/ TDF 300 mg/ FTC 200 mg	One tablet	Complera ($44.8643)	One tablet daily	$44.8643

3TC = lamivudine; ABC = abacavir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; RPV = rilpivirine TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Note: Prices sourced from Ontario Drug Benefit e-Formulary, accessed October 22, 2018.

When compared with other available single-tablet regimens, Delstrigo is less costly. One exception being EFV/TDF/FTC because of its available generics. However, when compared with the weighted-average cost relative to the market share of each single-tablet regimen in Ontario ($41.7230),[14] Delstrigo is less costly.

3.3 Manufacturer-Submitted Information Regarding Current Patent Status

Exclusivity for both products (DOR [single compound] and DOR/3TC/TDF FDC) are based on the DOR compound patent, CA 2794377, which expires March 2031.

3.4 Critical Appraisal of Cost Information

The manufacturer conducted a cost comparison analysis of DOR/3TC/TDF (Delstrigo) STR compared with other STRs for the complete regimen for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to DOR, 3TC, or tenofovir. At the submitted price of $28.79 per tablet, the manufacturer noted that DOR/3TC/TDF is less costly than the sum of its component medications based on publicly available drug prices in Ontario. Based on Ontario Drug Benefit Formulary prices for 3TC ($7.25) and TDF ($4.89) and the manufacturer's submitted price for DOR ($16.65), the manufacturer's combined STR is similar in price ($0.0022 less costly per day) to the individual component medications. CADTH identified variations in publicly available prices across jurisdictions of the backbone medications 3TC and TDF such that use of DOR/3TC/TDF may lead to cost savings or incremental costs compared with the individual components depending on the jurisdiction (DOR/3TC/TDF is more costly than the individual components in Yukon).

Additionally, the manufacturer presented a cost comparison of DOR/3TC/TDF with other STRs available in Canada. The clinical expert consulted by CADTH for this review considered these to be appropriate comparators for DOR/3TC/TDF, but noted that several relevant comparators were not included. As a result, CDR compared the cost of DOR/3TC/TDF with all STRs available on the market with similar Health Canada indications (Table 16).[14] CADTH identified that the Ontario Drug Benefit formulary price of EFV/TDF/FTC changed in October 2018; the updated price is reflected in Table 16. CADTH also identified that the components of several STRs were incorrectly reported in the manufacturer's cost comparison table — these have been corrected in Table 16.

DOR/3TC/TDF is between 17% and 45% less costly than regimens listed in Table 16, with the exception of EFV/TDF/FTC. DOR/3TC/TDF costs $17.46 (154%) more per day than EFV/TDF/FTC.

BIC/TAF/FTC and DTG/ABC/3TC are the only STRs included in the US DHHS guidelines as recommended initial regimens for most people with HIV.[4] While DOR/3TC/TDF is less costly

than these regimens based on the publicly available prices, it is currently recommended by the DHHS as initial treatment in certain clinical situations. According to the DHHS, "These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred."[4]

Table 16: Cost Information Comparing Manufacturer-Submitted Price With Other Available Single-Tablet Regimens

Drug/Comparator	Strength	Dosage Form	Price	Recommended Daily Use	Average Daily Drug Cost	% Difference in Cost
DOR/3TC/TDF[a] Delstrigo	100 mg / 300 mg / 300 mg	One tablet	$28.7900	One tablet daily	$28.79	
NNRTI-Based Regimens						
RPV/TAF/FTC Odefsey	25 mg / 25 mg /200 mg	One tablet	$42.3670	One tablet daily	$42.37	32%
RPV/TDF/FTC Complera	25 mg / 300 mg / 200 mg	One tablet	$44.8643	One tablet daily	$44.86	36%
EFV/TDF/FTC Atripla and generics	600 mg / 300 mg / 200 mg	One tablet	$11.3300	One tablet daily	$11.33	–154%
INSTI-Based Regimens						
DTG/ABC/3TC[b] Triumeq	50 mg / 600 mg / 300 mg	One tablet	$43.2020	One tablet daily	$43.20	33%
BIC/TAF/FTC Biktarvy	50 mg / 25 mg / 200 mg	One tablet	$39.2227[a]	One tablet daily	$39.22	27%
EVG/COBI/TAF/FTC Genvoya	150 mg / 150 mg / 10 mg / 200 mg	One tablet	$45.1440	One tablet daily	$45.14	36%
EVG/COBI/TDF/FTC Stribild	150 mg / 150 mg / 300 mg / 200 mg	One tablet	$48.0177	One tablet daily	$48.02	40%
INSTI Plus NNRTI						
DTG/RPV Juluca	50 mg / 25 mg	One tablet	$34.8677[c]	One tablet daily	$34.87	17%
Boosted PI-Based Regimens						
DRV/c/TAF/FTC Symtuza	800 mg / 150 mg / 10 mg / 200 mg	One tablet	$52.2670[c]	One tablet daily	$52.27	45%

3TC = lamivudine; ABC = abacavir; BIC = bictegravir; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Note: All prices are from the Ontario Drug Benefit e-Formulary, accessed January 24, 2019 unless otherwise specified.[15]

[a] In the manufacturer's table, the combination was listed as DOR/3TC/FTC. The combination actually contains TDF.

[b] CADTH noted that the price of the individual components (DTG plus ABC/3TC) was less than the price of the single-tablet regimen ($25.49). The annual cost of these two treatments used in combination is $9,303. At the price of the individual components, DOR/3TC/TDF is more costly than DTG plus ABC/3TC.

[c] Prices from Delta PA database, accessed January 24, 2019.[16]

Issues for Consideration

DOR/3TC/TDF can be taken with or without food, providing added convenience over some STRs that must be taken with food or on an empty stomach.[5]

The clinical expert also noted that DOR/3TC/TDF contains an older preparation of tenofovir, TDF, which has greater risk of renal toxicity and bone mineral density loss compared with a newer preparation of tenofovir, TAF. The expert noted that the backbone TDF might not be appropriate for some patients and therefore DOR would be used in combination with TAF-based backbone treatments, or TAF-based STRs would be used.

The individual component, DOR, is currently under CDR review.

Discussion

The Discussion and Conclusions sections were completed by the CDR reviewer. This review was conducted in tandem with the evaluation of the DOR single-dose product, (Pifeltro), which includes additional study data that are not presented in this report. However, this section provides an overall discussion pertaining to the evidence from the two relevant studies.

Summary of Available Evidence

The evidence base for this review was comprised of one double-blind trial (DRIVE-AHEAD) conducted in treatment-naive patients and one open-label trial (DRIVE-SHIFT) conducted in virologically suppressed treatment-switch patients. Both studies were randomized, active-controlled, noninferiority trials; with a base study period of 96 and 48 weeks for the double-blind and open-label studies, respectively. In DRIVE-AHEAD, the treatments administered were DOR/3TC/TDF or EFV/FTC/TDF. In DRIVE-SHIFT, patients either immediately switched to DOR/3TC/TDF to be received for 48 weeks (ISG) or continued their baseline regimen (RTV or COBI-boosted PI, or an integrase strand transfer inhibitor, or an NNRTI, each administered with two NRTIs) for 24 weeks before switching to DOR/3TC/TDF (DSG). The primary outcome in both trials was virologic suppression defined as the proportion of patients with HIV-1 RNA of fewer than 50 copies per mL (calculated using the FDA Snapshot algorithm). In DRIVE-AHEAD the between-treatment difference for the primary efficacy outcome was analyzed at week 48, while in DRIVE-SHIFT, the primary analysis compared the proportion of patients maintaining HIV-1 RNA of fewer than 50 copies per mL at 48 weeks for the ISG versus those maintaining this outcome at 24 weeks while on baseline regimen (DSG). The noninferiority margin was 10% and 8% for the double-blind and open-label trials, respectively. Notable safety end points included changes in lipid levels and neuropsychiatric AEs. Lastly, it should be noted that there is no evidence for use of a DOR-based regimen in patients who have failed to achieve virologic suppression on ART.

Interpretation of Results

Efficacy

The comparator chosen in DRIVE-AHEAD, namely EFV, even though available in Canada, is not the preferred choice of drug for treatment initiation according to the clinical expert consulted for this review. The DHHS guidelines[4] widely recognized for the management and treatment of HIV recommend the following treatment combinations in treatment-naive patients: BIC/TAF/FTC, DTG/ABC/3TC, DTG/tenofovir/FTC, RAL/tenofovir/FTC; with 3TC as an alternative to FTC and tenofovir used with consideration to bone and renal toxicities and lipid levels.[4] The clinical expert agreed that the aforementioned regimens, in addition to FTC/EVG/c/TAF (Genvoya), are the most relevant comparators from a Canadian perspective. In addition, an ARV regimen based on TAF is more desirable to clinicians and patients due to its relatively low bone and renal toxic profile compared with TDF. Notably, the DHHS guideline recommends DOR/TDF/3TC and DOR plus TAF/FTC as initial regimens in certain clinical situations, including patients with high cardiac risk and hyperlipidemia.[4]

For treatment-experienced patients with viral suppression, the DHHS guidelines do not provide a list of recommended therapies, rather the guidelines outline that selecting a new ART regimen should be based on patients' previous ART history, including virologic responses, past ART-associated toxicities and intolerances, resistance test results, drug-drug interactions, and pill burden, in addition other non-clinical considerations.[4] The baseline regimens for the treatment-switch patients in DRIVE-SHIFT, namely boosted PI, boosted EVG, or NNRTI, are relevant comparators in this setting.

The trial in treatment-naive patients (DRIVE-AHEAD) was conducted with good methodological rigour, with an appropriate statistical analyses plan, selection of trial population and outcomes, and adequate follow-up. The primary outcome in DRIVE-AHEAD was consistent with the FDA Snapshot algorithm, virologic suppression, i.e., HIV-1 RNA of fewer than 50 copies per mL at week 48. A number of design feature and methodological issues limited the validity and interpretability of the switch trial (DRIVE-SHIFT). The switch trial also used the proportion of patients with HIV-1 RNA of fewer than 50 copies per mL as the primary outcome, as opposed to the FDA-recommended outcome of virologic failure, i.e., HIV-1 RNA of 50 copies per mL or more at week 48.[9] Although the proportional difference in HIV-1 RNA of 50 copies per mL or more between the treatment groups was compared statistically; adjustment for multiple comparisons was not made. The reported result for the primary efficacy outcome showed the 8% noninferiority margin was met; however, the FDA Snapshot algorithm to account for missing data (missing data = failure) was not followed properly. Instead, some patients with missing data at week 48 had their blood samples reanalyzed from other sources and their data were added to the analyses data set post-hoc. Following this modification, the noninferiority margin was met for the primary efficacy outcome; however, noninferiority was not demonstrated with the true Snapshot approach. Finally, testing of primary and secondary end points in the statistical hierarchy was based on different periods of exposure for the two treatment groups. Patients in the ISG group received DOR/3TC/TDF for 48 weeks whereas those in the DSG group received their baseline regimens for weeks 0 to 24 and DOR/3TC/TDF for weeks 24 to 48. Statistical comparisons were not made between the treatment groups at week 24 for most end points (including the primary efficacy end point), or were not controlled for multiplicity. Instead, results for the ISG group at week 48 were compared with the DSG group at week 24.

Both trials met the a priori defined noninferiority margin (10% for treatment naive and 8% for treatment-switch trials) for the primary efficacy outcome, i.e., virologic success. The virologic success rates across trials were greater than 80% in treatment-naive patients and greater than 90% in treatment-switch patients by week 48. The higher response rate among treatment-switch patients is expected given that they achieved virologic suppression on a stable baseline regimen of ART at baseline. Among treatment-naive patients, the rate of discontinuation ranged between 13% and 17% at week 48, and between 18% and 24% at week 96. The primary causes for study discontinuation were AEs, lack of efficacy, lost to follow-up, and patient withdrawal. The manufacturer indicated the stringent criteria in place for study discontinuation as the possible reason for the high dropout rate and the subsequent lower virologic success rate. Patients who met the very stringent PDVF criteria (having a confirmed [i.e., two consecutive measures at least one week apart] HIV-1 RNA of 200 copies per mL or more at week 24 or week 36, or confirmed HIV-1 RNA of 50 copies per mL or more at week 48; or confirmed HIV-1 RNA 50 copies per mL or more after initial response of HIV-1 RNA of fewer than 50 copies per mL at any time during the study) had to discontinue the study. Under this rule, patients who experienced a viral rebound (i.e., confirmed HIV-1 RNA of 50 copies per mL or more after having been suppressed to fewer

than 50 copies per mL) during the study were required to discontinue. Other recent clinical trials used a higher threshold for PDVF: 200 to 400 copies per mL HIV-1 RNA. Additionally, the majority of the patients who met the PDVF criteria had fewer than 200 copies per mL HIV-1 RNA between the viral failure visit and the viral failure confirmation visit. It is possible that several patients could have been re-suppressed to fewer than 50 copies per mL had they been allowed to continue in the trial. Results using the observed failure (OF) approach, which excluded patients who discontinued for non-efficacy related reasons and therefore can be considered more reflective of viral efficacy, confirmed the findings and showed a higher response rate in both groups within the trials.

Despite the relatively lower virologic success rates among treatment-naive patients overall, patients receiving DOR had a numerically greater success rate at both weeks 48 and 96. Likewise, a lower proportion of patients receiving DOR had no virologic data available. These differences can be partially attributed to the lower discontinuation rate among the DOR recipients, resulting from lost to follow-up, non-compliance with study drug, and withdrawal by patient, as previously described.

Notably, the proportions of treatment-naive patients with HIV-1 RNA of 50 copies per mL or more were higher than expected according to the clinical expert, approximately 10% at week 48, and between 12% and 16% at week 96. Between-treatment differences were largely similar. It is unclear if all of the patients were classified appropriately according to the FDA Snapshot algorithm for this outcome given that patients lacking virologic data were not included as failures (assumption of HIV-1 RNA of 50 copies per mL or more). The impact this would have had on the results in uncertain.

Harms

The overall frequency of AEs among treatment-naive patients did not increase by much between week 48 and week 96 (overall incidence 82% to 91% at week 48 and 88% 94% at week 96). Treatment-naive patients experienced more AEs (range: 82% to 91%, data not presented) than treatment-switch patients (range: 52% to 81%) by week 48. Patients in the ISG group of DRIVE-SHIFT had an increased rate of AEs at week 24 compared with the baseline regimen at week 24 for the DSG group; a pattern consistent with the notion that patients switching therapies are likely to experience more AEs versus those remaining on their baseline therapy. Common AEs across trials included diarrhea, headache, upper respiratory tract infection, nausea, nasopharyngitis, pharyngitis, fatigue, back pain, bronchitis, cough, syphilis, upper abdominal pain, insomnia, dizziness, somnolence, abnormal dreams, and rash-related events. The frequency of SAEs was generally low among treatment-naive patients (5% to 9%), and even lower among treatment-switch patients (1% to 5%). Likewise, the frequency of withdrawals due to AEs was low (3% to 8%), with a lower rate reported for treatment-switch patients (less than 4%). A total of eight deaths were reported in the two trials, of which one incidence in DRIVE-SHIFT was considered to be related to the study drug (primary cause of death: myocardial infarction), although no confirmatory diagnosis (diagnosis by a medical professional or autopsy) was done.

DOR was also associated with a lower incidence of neuropsychiatric AEs; however, the benefits were largely in comparison with EFV, which is commonly associated with neuropsychiatric side effects.

Cost

The manufacturer submitted a cost comparison of drug costs for DOR/3TC/TDF versus its individual components, DOR, 3TC, and TDF. At the submitted daily price of $28.79, DOR/3TC/TDF is similar in cost ($0.0022 less costly per patient per day) than the sum of its individual components in most jurisdictions at the publicly available prices.

The manufacturer also compared DOR/3TC/TDF with other STRs marketed in Canada. CADTH noted that DOR/3TC/TDF is less costly than other STRs available in Canada with a similar indication, based on publicly available prices, apart from EFV/TDF/FTC, which is 39% of the submitted price of DOR/3TC/TDF. The clinical expert consulted by CADTH noted that DOR/3TC/TDF contains an older preparation of tenofovir, with greater potential for renal and bone toxicity, meaning that this combination may not be appropriate for use in some individuals.

Appendix 1: Drug Plan Listing Status for Individual Components

Table 17: Listing Status for Individual Components of the New Combination Product

Components	Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Doravirine	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB
Lamivudine	FB	FB	EX	FB	FB	FB	FB	FB	FB	FB	FB	–	–	–
Tenofovir disoproxil fumarate	FB	FB	EX	EX	EX	EX	FB	FB	EX	EX	EX	–	–	–

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

Appendix 2: Summary of Patient Input

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

One patient group, the Canadian Treatment Action Council (CTAC), provided input for this drug review. CTAC is a national non-governmental organization that focuses on access to treatment, care, and support for people living with HIV and hepatitis C. CTAC's organizational goals are to engage community members, service providers, policy-makers, and other relevant stakeholders to identify, develop, and implement policy and program solutions. Full CTAC membership is reserved for individual people living with HIV (including HCV coinfection) and organizations, groups, or projects with a substantial HIV mandate (including HCV coinfection). Associate CTAC membership is open to any individual, organization, group, or project that supports CTAC's mandate and objective.

In the past two years, CTAC has received funding in excess of $50,000 from ViiV Healthcare. CTAC did not receive help from outside the organization to prepare this submission, or to collect and analyze the data used in this submission.

2. Condition-Related Information

Data for this submission were obtained from seven patients with HIV (five men and two women) who attended a patient input consultation workshop in Toronto, Canada. The participants were in their twenties, forties, or fifties and had been receiving treatment for HIV for five to 34 years. In addition, survey data collected for a patient submission on dolutegravir was used to inform this patient submission.

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. Access, administration of, and adherence to highly active antiretroviral treatment can control the progression of HIV such that patients generally manage their condition as a chronic illness. However, patients with HIV are more susceptible to inflammation and non-infectious comorbidities, including bone fractures and renal failure, liver and cardiovascular disease. Many of those living with HIV experience negative mental health outcomes, whether as a side effect from treatment, or from facing stigma, discrimination, and related stress. Stigma is one of the more prominent issues dealt with, as explained by one respondent, "I still cannot come to terms with the fact that I'm HIV positive, and I've been positive for 25 years. I still run away from it, and I have a hard time talking about it…" This is further highlighted by another respondent from the dolutegravir RPV survey regarding their interaction with the medical community. "Local doctors feel ill-equipped to treat HIV due to inexperience because of low patient caseloads with the condition. Stigma also plays into it I think. Unless they're familiar, doctors still see HIV as something more difficult to live with than it actually is." Another respondent (from the dolutegravir RPV survey) discussed the challenge of managing HIV while residing in a rural area, "I live in a rural area and have to travel about 100 km each way for my doctor's appointments. I only see my doctor about every six months. Obviously if I had to travel that far more often it would be a challenge. For those who don't have the support of family this could definitely be an obstacle."

Many of those living with HIV experience intersecting vulnerabilities conditioned by the social determinants of health — the social and structural conditions in which people live, work, and are shaped by the distribution of money, power, and resources. Limited funding or services for addictions, mental health, housing, and food security can impact patients' HIV treatment. One respondent from the dolutegravir consultations noted that difficulties

understanding stigma and its impact, and navigating HIV-specific social services and institutional systems, including disability, insurance, and mortgage, have presented specific challenges. One respondent stated, “I am worried about the fact that HIV is now viewed as chronic, manageable disease. I still have good and bad days but, if HIV is now seen as something other than a disability, will I be forced to go back to work, even when I’m not well?”

Respondents all noted substantial impact on caregivers looking after patients living with HIV. One respondent highlighted that the challenges his/her spouse faces in providing support is surrounding disclosure. According to the respondent, “Hiding from friends and some of our family members that I am HIV positive has been extremely difficult and hindered the ability to acquire a social safety net” (from the dolutegravir survey).

3. Current Therapy-Related Information

Data for this submission were obtained from seven patients with HIV who were receiving treatment for the past five to 34 years. These patients had been on their current therapy for five to 10 years with minor changes to therapy that were made due to other health problems or resistance that developed.

As a result of being on HIV treatment, many participants described noticeable improvements in their quality of life and ability to engage in daily activities. Discussing the overall impact of treatment on his life, one participant stated, “Not only do I feel healthy, I know I am thanks to the HIV medication. Without it, I would be dead by now.” When asked whether treatment had improved their quality of life, another respondent answered, “In 1995, the doctors said I had 2 months to live, and that I’d better get my affairs in order. I never expected that I’d still be alive.” Another participant noted that, “My quality of life has improved. I’m now on a combination of drugs that has gotten me to an undetectable viral load.”

Respondents to the dolutegravir survey also indicated that their treatment was effective at suppressing their viral load; but some had experienced severe adverse effects to older treatments such as zidovudine.

CTAC stated that the increased risk of experiencing comorbidities associated with HIV may be, in part, due to antiretroviral treatments themselves. In addition, not all patients with HIV are able to achieve viral suppression despite trying multiple treatment regimens. Further, treatment adherence is necessary for therapy to be effective and to minimize the development of drug class resistance that would necessitate a change in therapy. CTAC stated that having the maximum possible treatment options is of clinical importance.

4. Expectations About the Drug Being Reviewed

None of the patients surveyed had experience with doravirine; however, many expressed an interest in a drug with a new chemical composition that may provide another treatment option if resistance to other treatments is a problem. Differences in drug-drug interactions or adverse events noted for doravirine compared with some other treatments were considered important to the patients surveyed.

One participant noted, “I like the fact that this medication has a new chemical composition. I like knowing the option is out there, since I am resistant to many, many of the current HIV drugs out there. My doctor told me, ‘The meds that you are on now are the last ones available that you can take.’” Another participant from the dolutegravir rilpivirine survey noted, “I don't see replacing the ‘devil’ I know with the ‘devil’ I don't know - at least on a personal basis. If I had to make changes - and that time could come since I've been on the present regime for quite some time.”

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