# NDA/BLA Multi-Disciplinary Review and Evaluation

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| **Application Type** | NDA |
| **Application Number(s)** | 210455 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | September 22, 2017 |
| **Received Date(s)** | September 22, 2017 |
| **PDUFA Goal Date** | July 22, 2018 |
| **Division/Office** | Division of Antiviral Products/Office Antimicrobial Products |
| **Review Completion Date** | See DARRTS electronic signature page |
| **Established Name** | darunavir, cobicistat, emtricitabine, and tenofovir alafenamide |
| **Trade Name** | SYMTUZA™ |
| **Pharmacologic Class** | Combination of darunavir, a human immunodeficiency virus (HIV-1) protease inhibitor, cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir alafenamide, both HIV-1 nucleos(t)ide analog reverse transcriptase inhibitors |
| **Applicant** | Janssen Products, LP |
| **Formulation(s)** | 800/150/200/10 mg fixed-dose combination tablets |
| **Dosing Regimen** | One tablet taken orally once daily with food |
| **Applicant Proposed Indication(s)/Population(s)** | Complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | Indicated as complete regimen for the treatment of HIV-1 infection in adults:<br>• who have no prior antiretroviral treatment history or<br>• who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir |

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

# Glossary

| | |
|---|---|
| AC | advisory committee |
| ADME | absorption, distribution, metabolism, excretion |
| ADR | adverse reaction |
| AE | adverse event |
| ARV | antiretroviral |
| ART | antiretroviral therapy |
| BRF | Benefit Risk Framework |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | Chemistry, manufacturing, and controls |
| COBI | cobicistat |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| DAIDS | Division of AIDS |
| DAVP | Division of Antiviral Products |
| DMC | data monitoring committee |
| DRV | darunavir |
| DRV/c | darunavir/cobicistat |
| D/C/F/TAF | darunavir/cobicistat/emtricitabine/tenofovir alafenamide fumarate |
| D/C/F/TDF | darunavir/cobicistat/emtricitabine/tenofovir disoproxil fumarate |
| DRV/r | darunavir/ritonavir |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| EVG/c | elvitegravir/cobicistat |
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide |
| E/C/F/TDF | elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| FDC | fixed dose combination |
| FTC | emtricitabine |
| F/TAF | emtricitabine/tenofovir alafenamide |
| F/TDF | emtricitabine/tenofovir disoproxil fumarate |
| GCP | good clinical practice |
| GRMP | good review management practice |

| | |
|---|---|
| HIV-1 | human immunodeficiency virus type-1 |
| ICH | International Conference on Harmonization |
| IND | Investigational New Drug |
| INSTI | integrase strand transfer inhibitor |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NDA | new drug application |
| NME | new molecular entity |
| NRTI | nucleos(t)ide reverse transcriptase inhibitor |
| NNRTI | non- nucleos(t)ide reverse transcriptase inhibitor |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | protease inhibitor |
| PI/c | cobicistat with a protease inhibitor |
| PI/r | ritonavir with a protease inhibitor |
| PK | pharmacokinetics |
| PMC | post-marketing commitment |
| PMR | post-marketing requirement |
| popPK | population PK |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| RAMs | resistance-associated mutations |
| RAS | resistance-associated substitution |
| RelBA | relative bioavailability |
| REMS | risk evaluation and mitigation strategy |
| RT | reverse transcriptase |
| RTV | ritonavir |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard-of-care |
| TAF | tenofovir alafenamide |

| | |
|---|---|
| TDF | tenofovir disoproxil fumarate |
| TFV | tenofovir |
| TEAE | treatment-emergent adverse event |
| TEADR | treatment-emergent adverse reaction |
| TN | treatment-naïve |
| US | United States |
| USPI | US prescribing information |

# 1 Executive Summary Division Level Concurrence

This NDA for darunavir (DRV), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF) of D/C/F/TAF fixed-dose combination (FDC) tablet for oral use is submitted by Janssen Products, LP. The NDA contains four non-new molecular entities (non-NMEs). Each non-NME is an approved product and is available as either a single tablet (DRV, COBI, FTC) or as part of various FDCs. This NDA has been reviewed by the multi-disciplinary review team, each discipline has recommended approval of this NDA, and I concur with those recommendations. D/C/F/TAF tablets will be approved as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.

Janssen submitted two adequate and well-controlled trials that provide substantial evidence of efficacy for the indication approved. D/C/F/TAF is safe for its intended use. We concur that identified risks can be mitigated through labeling and further evaluated during routine pharmacovigilance. The overall benefit/risk assessment is favorable. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Uni-Review document, the Quality Assessment Review, and the Benefit Risk Summary.

## 1.1. Product Introduction

SYMTUZA is a fixed-dose combination (FDC) tablet that contains four non-new molecular entities (non-NMEs), darunavir (DRV), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF), or D/C/F/TAF. DRV is an HIV-1 (hereafter referred to as HIV) protease inhibitor (PI); COBI is a CYP3A inhibitor; and FTC and TAF are a nucleos(t)ide reverse transcriptase inhibitors (NRTIs). The Applicant's proposed indication is a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. The Applicant's proposed recommended dosage is one tablet taken once daily with food in patients 12 years and older (b) (4)

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Application contains substantial evidence of effectiveness required by law 21 CFR 314.126(a)(b) to support approval of D/C/F/TAF as a complete regimen for the treatment of HIV-1 infection in adults:

- who have no prior antiretroviral treatment history; or

- who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.

Phase 3 trials AMBER and EMERALD evaluated D/C/F/TAF as a complete regimen in treatment-naïve and virologically suppressed HIV-infected adults, respectively. In the AMBER trial, HIV RNA < 50 copies/mL at Week 48, considered an adequate and durable virologic response in treatment-naïve patients, was achieved in 91% versus 88% of participants in the D/C/F/TAF and D/C/F/tenofovir disoproxil fumurate (TDF) groups, respectively, with a treatment difference of 2.7% [95% confidence interval (CI): -1.6, 7.1]. In the EMERALD trial, preservation of virologic suppression was adequate, as 0.8% versus 0.5% of participants in the D/C/F/TAF and active control groups, respectively, experienced virologic failure defined as HIV RNA > 50 copies/mL at Week 48, with a treatment difference of 0.3% (95% CI: -0.7, 1.2). The pre-specified noninferiority margins of -10% in the AMBER trial and 4% in the EMERALD trial were met, supporting non-inferiority of D/C/F/TAF to the respective active control in each trial for treatment of HIV in treatment-naïve or virologically suppressed adults. The EMERALD trial results also support efficacy in virologically suppressed patients with prior virologic failure, specifically with evidence of FTC resistance. Efficacy results from other subgroup analyses were consistent with the overall findings.

The Application does not contain substantial evidence to support approval of D/C/F/TAF for pediatric patients ages 12 years to less than 18 years because:

- No trials were conducted with D/C/F/TAF in pediatric patients;
- Final study results from an ongoing pediatric trial to support safety and effectiveness of COBI-boosted DRV (DRV/c) are not yet available; and
- Completed pediatric trials with TAF 10 mg in combination with COBI and elvitegravir (EVG/c), an integrase strand transfer inhibitor (INSTI), should not be leveraged to establish effectiveness of TAF 10 mg in the presence of COBI and a PI (PI/c; e.g., DRV/c) because TAF exposures are different in the presence of EVG/c compared to DRV/c.

To demonstrate substantial evidence of effectiveness of D/C/F/TAF in ages 12 years to less than 18 years, the Applicant must specifically demonstrate effectiveness in this population with: (1) DRV coadministered with COBI; and (2) TAF 10 mg coadministered with PI/c or PI/ritonavir (PI/r).

### 1.3. Benefit-Risk Assessment

D/C/F/TAF contains four non-new molecular entities (non-NMEs), and the benefit-risk of each approved component was evaluated in prior NDA reviews. However, D/C/F/TAF FDC differs from currently available products with respect to TAF exposures. First, construction of a similar regimen with DRV/c 800 mg/150 mg and F/TAF 200 mg/25 mg is currently possible, but that

combination results in higher TAF exposures due to a higher TAF dose compared to D/C/F/TAF 800 mg/150 mg/200 mg/10 mg; thus, a relative bioavailability trial with available components is inadequate. Similarly, TAF 10 mg as a component of currently approved EVG/c/F/TAF (E/C/F/TAF) results in higher TAF exposures compared to D/C/F/TAF. Thus, extrapolation of safety from prior E/C/F/TAF trials to D/C/F/TAF in terms of durability of virologic response and potential for development of resistance is inadequate. The AMBER and EMERALD trials fill this gap, and the benefit-risk of D/C/F/TAF 800 mg/150 mg/200 mg/10 mg FDC as a complete regimen based on these trial results is summarized below. Of note, a benefit-risk framework table was not completed because extrapolation of benefit-risk of the other three components (DRV, COBI, and FTC) from prior trials is adequate.

Overall, 91% of treatment-naïve participants achieved virologic success (HIV RNA <50 copies/mL) in the AMBER trial, and 0.8% of virologically suppressed participants at baseline experienced virologic failure (HIV RNA >50 copies/mL) in the EMERALD trial. These results demonstrate high efficacy and durable virologic response with no increased risk of resistance-associated substitutions with the lower TAF exposures and more specifically with D/C/F/TAF as a complete regimen in the indicated populations.

The major safety findings in this review were rash and increased LDL cholesterol, total cholesterol, and triglycerides from baseline. However, TAF appears to have a more favorable safety profile with respect to renal and bone safety compared to TDF. These findings are consistent with prior trials evaluating DRV and ritonavir (DRV/r) and/or TAF.

In conclusion, the benefit-risk of D/C/F/TAF is comparable to currently available regimens constructed with the same or similar individual components (e.g., DRV/r or DRV/c with F/TAF or F/TDF), despite lower TAF exposures. D/C/F/TAF is the first PI-based complete regimen available in a single tablet, which offers convenience to patients and is a potential benefit over currently available PI-based regimens that require two or more tablets. Overall, the benefit-risk profile of D/C/F/TAF is favorable.

### 1.4. Patient Experience Data

No patient experience data were submitted in the NDA.

### 1.5. Overall Conclusions and Recommendations

Approval of D/C/F/TAF as a complete regimen for the treatment of HIV-1 infection in adults who have no prior antiretroviral treatment history or who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir is fully supported by the available evidence of efficacy and safety.

# 2 Therapeutic Context

## 2.1. Analysis of Condition

The World Health Organization (WHO) states approximately 37 million people were living with HIV globally in 2016. In the United States (US), at the end of 2015, an estimated 1.1 million persons aged 13 or older were living with HIV infection, including an estimated 162,500 persons whose infections had not been diagnosed. Additionally, as reported by the Centers for Disease Control (CDC), the number of new HIV-1 infections in the US in 2016 was 39,782 among adults and children.

The goal of HIV treatment is to durably suppress HIV RNA, preserve and restore the immune system, and reduce HIV-associated morbidity. ART has provided HIV-infected patients with improved long-term survival. Effective viral load suppression can also provide the public health benefit of decreased HIV transmission.

Treatment of HIV infection has dramatically improved since the mid-1990s, after the introduction of the use of highly active ART. Despite such progress, the need continues for development of new ARV drug products, new fixed dose combination (FDC) products, and new regimens because of the ongoing epidemic in parts of the world. A need for better tolerated regimens also exists. The introduction of FDC drug products has allowed for simpler ARV regimens, increasing the likelihood of adherence and thereby improving treatment outcomes. Availability of new regimens such as complete three drug regimen FDCs have also allowed patients to switch if they are not tolerating their current regimens or have 'pill fatigue' from multiple pill regimens. For example, according to a publication by the Antiretroviral Therapy Cohort Collaboration (2013), among the 21,000+ patients in a European and North American cohort who were on their first combination ARV regimen, more than half modified or interrupted their first regimen because of either adverse events or toxicities of the ARVs, desire for regimen simplification, or patient choice. These observations suggest a need for continued development of new products and/or regimens and that complete regimen FDCs may be convenient for patients with HIV/AIDS.

## 2.2. Analysis of Current Treatment Options

Each component of SYMTUZA (DRV, COBI, FTC, and TAF) is approved as a single agent and/or as part of a FDC product, and each product is generally indicated in combination with other antiretroviral (ARV) agents for the treatment of HIV infection. The most relevant products and FDA approval dates are as follows:

- EMTRIVA® (FTC) 200 mg capsule received FDA approval on July 2, 2003.

- PREZISTA® (DRV) 800 mg tablet received FDA approval on December 13, 2010.
- TYBOST® (COBI) 150 mg tablet received FDA approval on September 24, 2014.
- PREZCOBIX® (DRV/c) 800 mg/150 mg received FDA approval on January 29, 2015.
- DESCOVY® (F/TAF) 200 mg/25 mg tablet received FDA approval on November 10, 2016.

Excluding fixed-dose combination products and different formulations, 28 individual ARV drugs and two drugs used as pharmacokinetic (PK) enhancers with ARVs are approved and available for the treatment of HIV-1. Ritonavir (RTV) is not counted as an ARV used for treatment of HIV because it is used in therapy as a PK enhancer. Currently, ART for treatment of HIV infection in treatment-naïve or treatment-experienced patients, without history of virologic failure, is generally comprised of combining at least three antiretroviral (ARV) medications, two NRTIs plus either a non-nucleoside reverse transcriptase inhibitors (NNRTI), PI, or integrase strand transfer inhibitor (INSTI). A two-drug regimen consisting of an NNRTI and an INSTI (NRTI-sparing) is also approved for treatment of HIV in virologically suppressed patients.

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

SYMTUZA (D/C/F/TAF) contains four non-NMEs but is not currently marketed in the US as a FDC product.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

**On October 18, 2011,** Gilead Sciences, Inc., submitted a new IND for D/C/F/TAF FDC tablet (IND 113456) while TAF (formerly GS-7340) was under development in Phase 1 trials. Gilead conducted the initial development of D/C/F/TAF and transferred IND sponsorship to Janssen Research & Development **on October 16, 2014,** after submitting an End-of-Phase 2 meeting request and the background package. Janssen is responsible for regulatory approval, manufacturing, registration, distribution, and commercialization of the product worldwide.

The D/C/F/TAF development program is based on six clinical trials conducted with the FDC tablet in adults:

- Three completed Phase 1 trials, of which two were conducted by Janssen and one by Gilead;
- One completed supportive Phase 2b trial in HIV-infected, ARV-naïve participants (Study GS-US-299-0102; primary analysis at Week 24 and final analysis at Week 48) conducted by Gilead to evaluate the safety and efficacy of D/C/F/TAF FDC versus DRV/c plus F/TDF; and
- Two ongoing pivotal Phase 3 trials (AMBER and EMERALD; primary analysis at Week 48) conducted by Janssen.

**On October 22, 2014**, an End-of-Phase 2 (EOP2) meeting (via teleconference) was held with Janssen to discuss the design of the proposed Phase 3 trial (EMERALD trial) and the adequacy of 24-week data from the switch trial along with a bioequivalence (BE) trial and Phase 2b trial (GS-US-299-0102) to support approval of D/C/F/TAF for the treatment of HIV-1 infection in adults. In summary, FDA provided the following comments to Janssen either at the EOP2 meeting or as follow-up to the EOP2 meeting (as late as March 30, 2015).

- A BE trial may be used for approval provided exposure of all components of D/C/F/TAF are bioequivalent to approved reference drugs for which we have safety and efficacy data. Note: PK data from GS-US-299-0101 indicated exposure of TAF 10 mg as part of D/C/F/TAF is not BE to the reference TAF products for which efficacy has been demonstrated.

- In the absence of established BE, the proposed switch trial will not be acceptable as the only well-controlled trial, and the Phase 2b trial is not adequate to serve as the confirmatory

clinical trial. FDA recommended one Phase 3 trial in treatment naïve patients if the study is well powered.

- FDA informed Janssen that virologic rebound (HIV RNA ≥50 copies/mL) should be the primary endpoint of the switch trial as a more informative efficacy comparison than the usual snapshot analysis of treatment success in this population. FDA also recommended a narrower non-inferiority (NI) margin (e.g., 3-4%). Janssen agreed and stated they would assess virologic rebound through the Week 48 window. Note: FDA did not clarify at the time that the virologic rebound endpoint should be assessed in the 48-week snapshot analysis window.

**On December 19, 2014**, Janssen submitted an initial pediatric study plan (iPSP), and FDA issued an agreed iPSP on June 30, 2015.

**On March 18, 2015**, Janssen submitted a new Phase 3 protocol, the AMBER trial.

**On December 20, 2016**, Janssen requested a pre-NDA meeting to discuss and seek concurrence from the Agency regarding the proposed content and format of the NDA submission in support of the registration of the D/C/F/TAF FDC tablet for the treatment of HIV-1 infection. In advance of the meeting, preliminary comments were sent to the Sponsor on February 10, 2017; however, the Sponsor canceled after receiving FDA's preliminary comments.

**On September 22, 2017**, Janssen submitted NDA 210455 for SYMTUZA.

# 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

Clinical sites in the US with the highest number of enrolled subjects (9-40 subjects) in the AMBER or EMERALD trial were considered for inspection. However, these sites either had recently undergone an inspection (within the last 1-2 years) without major findings or were difficult to access due to recent hurricanes in the area. Remaining clinical trial sites had too few enrolled subjects to impact trial results. Thus, clinical site inspections were not conducted for this NDA.

## 4.2. Product Quality

Novel excipients: No
Any impurity of concern: No
Sufficient controls to insure safety and efficacy of the commercial product: Yes

Each SYMTUZA tablet contains darunavir ethanolate equivalent to 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine (FTC), and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide (TAF). The yellow to yellowish-brown, capsule-shaped, film-coated tablet is debossed with "8121" on one side and "JG" on the other side. The quantitative composition of the tablet is listed in the Applicant's table below. See FDA product quality review for additional details.

**Table 1 Symtuza FDC Composition**

Table 1: Qualitative and Quantitative Composition of the Drug Product

| Component | Quality Reference[a] | Function | Quantity/Unit Dose (mg/tablet) |
|---|---|---|---|
| (b) (4) | | | |

# 5 Nonclinical Pharmacology/Toxicology

No nonclinical safety studies were submitted with this supplement. A comprehensive review of the nonclinical safety studies (including the reproductive and developmental toxicology studies) for SYMTUZA has been conducted under NDA 21976 (Darunavir), NDA 203094 (Cobicistat), NDA 21500 (Emtricitabine), or NDA 208464 (Tenofovir alafenamide). Refer to original Pharmacology/Toxicology review for the individual agents for further pharmacology/toxicology information.

PLLR-related language was included in Section 8 of the product labeling and deemed appropriate with the agreed upon changes.

# 6 Clinical Pharmacology

**Reviewed Studies**

We reviewed six studies containing human PK data and two popPK modeling analyses (DRV and TAF). Study conduct and results were acceptable (see section 15.2 Clinical Pharmacology Individual Study Reviews). These studies and analyses impacted clinical pharmacology-related labeling with regard to food effect, tablet splitting, and the effect of demographic factors on PK (Table 2).

**Adolescent Indication**

See section Pediatrics.

**Drug Interactions and Labeling**

No drug interaction studies were submitted. Drug interaction labeling for DRV and COBI were obtained verbatim from PREZCOBIX labeling (DRV and COBI) and drug interaction labeling for TAF are consistent with GENVOYA labeling (E/C/F/TAF). FTC is not subject to drug interactions.

The components of D/C/F/TAF were approved prior to submission of this NDA. Much of the labeling in the Drug Interactions and Pharmacokinetics sections were obtained from other product labelings. The applicant submitted right of reference letters to Gilead product labeling and we confirmed with Gilead that the right of reference letters allow for reproduction of labeling from Gilead-sponsored products in D/C/F/TAF labeling.

**Food Effect**

We agree with the applicant's proposal that D/C/F/TAF should be administered with food. In Phase 3 studies, subjects were instructed to take D/C/F/TAF with food, and the studies were successful.

**Tablet Splitting**

In Study TMC114FD2HTX1004, the PK of DRV, COBI, FTC, and TAF were evaluated in healthy subjects after administration of a whole vs split D/C/F/TAF tablet. Exposures of the components of D/C/F/TAF were similar between the whole and split tablet. We agree with proposed labeling that states the D/C/F/TAF can be split into two.

**Table 2.** Reviewed studies and analyses containing D/C/F/TAF PK data and impact on proposed labeling.

| Study # or analysis | Phase | D/C/F/TAF formulation | Primary objectives | Study included in DRV or TAF popPK model? | Impact on clinical pharmacology labeling |
|---|---|---|---|---|---|
| TMC114FD2HTX1004 | 1 | G001 | RelBA of whole vs split vs crushed tablet | No | The SYMTUZA tablet can be split |
| TMC114FD2HTX1002 | 1 | G001 | RelBA of FTC and TAF as D/C/F/TAF vs E/C/F/TAF<br><br>RelBA of D/C/F/TAF vs single agents<br><br>Effect of food on D/C/F/TAF | TAF | Take SYMTUZA with food |
| TMC114FD2HTX1001 | 1 | G001 | RelBA of D/C/F/TAF vs single agents | TAF | Included in DRV and/or TAF popPK model. Labeling regarding the effect of demographic factors on PK was drawn from the popPK analyses. |
| GS-US-299-0102 | 2 | Phase 2 | Efficacy, safety | TAF | |
| TMC114FD2HTX3001 | 3 | G001 | | DRV | |
| TMC114IFD3013 | 3 | G001 | | DRV | |
| DRV popPK analysis | 1, 2, 3 | NA | Predict exposures in phase 3 subjects, evaluate the effect of covariates on PK | NA | No effect of adult age, race, or gender on the PK of DRV or TAF |
| TAF popPK analyisis | 1, 3 | NA | | NA | |

G001 = commercial formulation; NA = not applicable; popPK = population pharmacokinetic; RelBA = relative bioavailability

# 7 Statistical and Clinical Evaluation

## 7.1. Sources of Clinical Data and Review Strategy

### 7.1.1. Table of Clinical Studies

Two Phase 3 studies were submitted in this NDA. Study TMC114FD2HTX3001 (AMBER trial) evaluates the efficacy and safety of D/C/F/TAF in HIV infected and treatment naïve patients, while Study TMC114IFD3013 (EMERALD Trial) evaluates the efficacy and safety of this same drug in HIV infected, treatment experienced, and virologically suppressed patients. Summary of the studies is provided in the following table (Table 3).

**Table 3. Listing of Phase 3 Clinical Trials Reviewed**

| Trial Identity | Trial Design | Study Population | Pre-specified Non-inferiority (NI) margin | Interim Analysis | Study Primary Endpoints | Statistical Method | Randomized Treatment Groups and Sample Sizes |
|---|---|---|---|---|---|---|---|
| TMC114FD2HTX 3001 (AMBER trial) | Randomized (1:1), double-blind, active controlled, Phase 3 non-inferiority trial | HIV-1 infected, treatment naïve patients | -10% | 2 planned interim analyses: Blinded sample size re-estimation; Futility analysis | The proportion of subjects who achieved HIV-1 RNA <50 copies/mL as defined by the FDA snapshot approach at Week 48 | Stratum-adjusted Mantel-Haenszel (MH) risk difference (stratified by HIV-1 RNA level: ≤100,000 vs. >100,000 copies/mL; CD4+ cell count: <200 vs. ≥200 cells/μL). | D/C/F/TAF arm: N=362 Control arm: N=363 |
| TMC114IFD3013 (EMERALD Trial) | Randomized (2:1), open-label, active controlled, Phase 3 non-inferiority trial | HIV-1 infected, treatment experienced, virologically suppressed patients | 4% | 3 planned interim analyses: Blinded sample size re-estimation; Futility analysis; Formal Week 24 sponsor-unblinded analysis | The proportion of subjects with virologic rebound at Week 48 | Stratum-adjusted Mantel-Haenszel (MH) risk difference (stratified by bPI use) | D/C/F/TAF arm: N=763 Control arm: N=378 |

#### 7.1.2. Review Strategy

**Data Sources**

The patient level datasets for AMBER and EMERALD trials analyzed in this review can be found at the following link in the Agency's electronic document room:

\\cdsesub1\evsprod\NDA210455\0000\m5

In addition to patient level datasets, other materials reviewed included the study protocols, statistical analysis plans, and clinical study reports.

**Data and Analysis Quality**

The data submitted in this NDA were used to reproduce the applicant's major efficacy and safety results. The protocol amendments and statistical analysis plan were sufficient, and the reported analyses were consistent with the planned analyses.

### 7.2. Review of Relevant Individual Trials Used to Support Efficacy

#### 7.2.1. AMBER Trial

**Trial Design and Endpoints**

AMBER trial was titled "A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination co-administered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects."

Adult patients with HIV infection, who were ARV treatment naïve, were randomized 1:1 to D/C/F/TAF arm or active control arm. Randomization was stratified by HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) and by CD4+ cell count (<200 cells/µL or ≥200 cells/µL) at screening. The primary objective of the study was to demonstrate that the efficacy of D/C/F/TAF FDC tablet was non-inferior compared to DRV/COBI FDC co-administered with FTC/TDF FDC.

The study included a screening phase, a 48-week double blind treatment phase, followed by another 48-week single arm, open label treatment phase. After Week 96, patients were given opportunity to continue the treatment for an extended period until the drug is commercially available, or the program be terminated by the company (Figure 1). The efficacy evaluation occurred when all patients completed 48 weeks of treatment. Week 96 data and analysis will be submitted later when available.

Study drug was administered as follows:

- D/C/F/TAF Arm: Regimen of a single tablet containing DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (D/C/F/TAF FDC) once daily, (n=335) + DRV/COBI FDC-matching and FTC/TDF FDC-matching placebo tablets once daily; and

- Control Arm: Regimen of DRV 800 mg/ COBI 150 mg FDC co-administered with FTC 200 mg/ TDF 300 mg FDC once daily, (n=335) + D/C/F/TAF FDC-matching placebo tablet once daily.

**Figure 1: Schematic Overview of AMBER Trial**

Baseline (Day 1) [a] — Week 24 DMC [b] — Week 48 [c,d] Primary analysis — Week 96 [e] Analysis

| Screening | Double-Blind Treatment Phase [f] | Single-arm Treatment Phase [c,d,f] | Extension Phase [e] | Follow-up |
|---|---|---|---|---|
| ≤ 30 days prior to baseline | **Treatment arm 1 (Test)** (n=335): D/C/F/TAF FDC once daily [g] DRV/COBI FDC-matching and FTC/TDF FDC-matching placebo tables once daily [g] | D/C/F/TAF FDC | D/C/F/TAF FDC | **ESTD [f] and 30-day FU visit [h]** |
| | **Treatment arm 2 (Control)** (n=335): DRV/COBI FDC coadminsitered with FTC/TDF FDC once daily [g] D/C/F/TAF FDC-matching placebo tablet once daily [g] | | | |

[a] Following the baseline visit, subjects will return for study visits at Weeks 2, 4, 8, 12, 24, 36, 48, and every 12 weeks thereafter until and including a Week 96 visit.

[b] Formal DMC interim analyses will be performed for monitoring purposes, including a futility analysis for lack of non-inferior) efficacy and a blinded sample size re-estimation.

[c] Subjects will continue to take their blinded study drug and to attend visits every 12 weeks following Week 48 until treatment assignment is unblinded.

[d] After unblinding, provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, all subjects will receive D/C/F/TAF treatment during a single-arm treatment phase up to Week 96. Subjects from the control arm who switch to the D/C/F/TAF regimen after the 48-week double blind treatment will be required to return to the clinic for an additional visit 3 to 7 weeks after the unblinding visit.

[e] After Week 96, subjects will be given the opportunity to continue D/C/F/TAF treatment during an extension phase until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development. During the extension phase subjects will attend visits every 6 months.

[f] Subjects who prematurely discontinue, either during the double-blind treatment phase (from Day 1 to Week 48) or during the single-arm D/C/F/TAF treatment phase (between Week 48 and Week 96) will be required to complete the ESTD assessments within 72 hours of stopping study treatment.

[g] All study drugs and matching placebo tablets must be administered orally, once daily in the morning with food, at approximately the same time each day.

[h] Any subject who has an ongoing AE or SAE at the time of his/her last study visit will be required to return to the clinic 30 days after the completion their his/her study visit for a 30-day FU visit (unless consent is withdrawn).

Source: AMBER trial protocol Figure 1.

Virologic responses were evaluated at Week 48. A favorable virologic response means that the patient serum HIV-1 RNA level < 50 copies/mL. The primary endpoint was the proportion of subjects who had HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot analysis, which is a recommend endpoint by HIV-1 drug development guidance[1]. Secondary endpoints included the proportion of subjects with HIV-1 RNA <20 and 200 copies/mL at Week 48; change from baseline in $\log_{10}$HIV-1 RNA and CD+4 cell count at Week 48.

**Key Inclusion and Exclusion Criteria**

Patients enrolled in this study were required to meet the following eligibility criteria:

- ARV treatment-naïve; no prior use of any approved or experimental anti-HIV drug for any length of time
- Screening plasma HIV-1 RNA level ≥1,000 copies/mL
- CD4+ cell count >50 cells/$mm^3$
- Screening HIV-1 genotype report had to show full sensitivity to DRV, tenofovir (TFV) and emtricitabine (FTC)
- Screening $eGFR_{CG}$ ≥70 mL/min

Key exclusion criteria were:

- Diagnosed with a new acquired immunodeficiency syndrome (AIDS)-defining condition within 30 days prior to screening
- Had proven or suspected acute hepatitis within 30 days prior to screening
- Hepatitis C antibody positive (however, spontaneously cured hepatitis C virus infection and subjects cured of HCV infection after treatment were allowed to participate)
- Hepatitis B surface antigen (HBsAg) positive
- History of cirrhosis

**Statistical Analysis Plan**

The primary analysis population was the intent-to-treat (ITT) population, which includes all subjects who were randomized and received at least 1 dose of study treatment.

The proposed method for the primary analysis was stratum-adjusted Mantel-Haenszel difference of the two treatment arms (D/C/F/TAF – active control) in the proportions of patients who had HIV-1 RNA < 50 copies/mL. The stratification factors were HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) and CD4+ cell count (<200 cells/µL or ≥200

[1] Food Drug Administration, Center for Drugs Evaluation Research (November 2015). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm355128.pdf

cells/µL). Exact 95% confidence interval (CI) of the difference in the proportions was calculated using Clopper-Pearson method. Non-inferiority of D/C/F/TAF FDC tablet to DRV/COBI FDC co-administered with FTC/TDF FDC was to be claimed if the lower limit of the 95% CI was greater than the pre-specified NI margin of -10%[2].

The planned sample size for AMBER trial was 670 (1:1 randomization) for a 90% power. This was calculated assuming both treatment arms had a response rate of 80% at Week 48, with a NI margin of -10% and one-sided significance level of 0.025.

Two interim analyses were planned. The first interim analysis was for a blinded sample size re-estimation when 445 patients were enrolled, and at least 30% of them reached Week 12 and 1% reached Week 24. It was planned that if the overall Week 48 response rate was lower than 0.6, an increase of sample size by 120 patients would be necessary to maintain the study power at 80%. No sample size increase occurred based on the results of the interim analysis. The second interim analysis was for a formal futility analysis to evaluate the efficacy of D/C/F/TAF regimen using conditional power. This happened when 725 subjects were enrolled, of which at least 89% reached Week 24 and 5% reached Week 48. The futility analysis was guided by an independent Data Monitoring Committee (DMC), while sponsor and study team remained blinded.

The efficacy was evaluated at one-sided 0.025 alpha level. No adjustment of p-value was performed to account for the interim analysis.

**Protocol Amendments**

[2] Food Drug Administration, Center for Drugs Evaluation Research (November 2015). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm355128.pdf

The protocol had two amendments. Neither amendment made substantial change to the study design or statistical analysis plan after randomization was started.

**Patient Disposition**

A total of 725 patients were randomized to the study. The majority of subjects completed 48 weeks of study treatment. The treatment discontinuation rates were similar in the two treatment groups, and the reasons for the pre-mature discontinuation were generally balanced between the two groups (Table 4).

**Table 4: Subject Disposition at Week 48, AMBER Trial**

| | D/C/F/TAF | Control |
|---|---|---|
| Randomized | 362 | 363 |
| Completed study treatment at Week 48 | 339 (93.6%) | 335 (92.3%) |
| Pre-maturely discontinued study treatment | 23 (6.4%) | 28 (7.7%) |
| Adverse event | 8 (2.2%) | 15 (4.1%) |
| Death | | 1 (0.3%) |
| Lost to follow-up | 5 (1.4%) | 5 (1.4%) |
| Non-compliance with study drug | 1 (0.3%) | |
| Physician decision | 3 (0.8%) | |
| Withdrawal by subject | 4 (1.1%) | 6 (1.7%) |
| Other | 2 (0.6%) | 1 (0.3%) |

Source: Reviewer's analysis.

**Protocol Violations/Deviations**

ITT population included patients who had predefined major protocol deviations, such as violated inclusion or exclusion criteria, received wrong dose or dose interrupted for more than 4 weeks, took disallowed concomitant medication, and non-compliance with study procedures. A total of 41 subjects had major protocol deviations (Table 5). No systematic protocol violations or deviations were observed at center level or at study level based on the study report. "Other" protocol deviations were diverse, balanced between groups, and either clinically insignificant and/or would not impact overall results.

**Table 5: Major Protocol Deviations, AMBER Trial**

| | D/C/F/TAF | Control | Total |
|---|---|---|---|
| Analysis set: Intent-to-treat, N | 362 | 363 | 725 |
| Subjects with major protocol deviations | 19 (5.2%) | 22 (6.1%) | 41 (5.7%) |
| Entered but did not satisfy criteria | 3 (0.8%) | 8 (2.2%) | 11 (1.5%) |
| Received wrong treatment or incorrect dose | 0 | 2 (0.6%) | 2 (0.3%) |
| Developed withdrawal criteria but not withdrawn | 0 | 1 (0.3%) | 1 (0.1%) |
| Other | 16 (4.4%) | 13 (3.6%) | 29 (4.0%) |

Note: Subjects may appear in more than one category

Source: AMBER trial CSR Table LSIDEV01.

**Demographic Characteristics**

The majority of the randomized subjects were male (88.3%), white (82.8%), ≤ 50 years of age (90.6%), with non-Hispanic background (86.3%), and were enrolled outside of US (81.7%). Demographic characteristics were generally balanced between the two treatment groups (Table 6).

**Table 6: Demographic characteristics, AMBER trial**

| | Statistic | Total (N=725) | D/C/F/TAF (N=362) | Control (N=363) |
|---|---|---|---|---|
| Age (Year) | | | | |
| | Mean | 35.3 | 35.6 | 35.1 |
| | SD | 10.08 | 10.17 | 9.99 |
| | Median | 34 | 34 | 34 |
| | Min, Max | 18.0, 71.0 | 19.0, 61.0 | 18.0, 71.0 |
| Age Group | n (%) | | | |
| <=50 | | 657 (90.6) | 326 (90.1) | 331 (91.2) |
| >50 | | 68 (9.4) | 36 (9.9) | 32 (8.8) |
| Sex | n (%) | | | |
| Male | | 640 (88.3) | 318 (87.8) | 322 (88.7) |
| Female | | 85 (11.7) | 44 (12.2) | 41 (11.3) |
| Race | n (%) | | | |
| White | | 600 (82.8) | 300 (82.9) | 300 (82.6) |
| Black | | 80 (11.0) | 40 11.0) | 40 (11.0) |
| Asian | | 11 ( 1.5) | 4 (1.1) | 7 (1.9) |

| | Statistic | Total (N=725) | D/C/F/TAF (N=362) | Control (N=363) |
|---|---|---|---|---|
| Other | | 27 (3.7) | 15 (4.1) | 12 (3.3) |
| Missing | | 4 (0.6) | 2 (0.6) | 2 (0.6) |
| Ethnicity | n (%) | | | |
| Hispanic or Latino | | 95 (13.1) | 50 (13.8) | 45 (12.4) |
| Not Hispanic or Latino | | 626 (86.3) | 310 (85.6) | 316 (87.1) |
| Missing | | 4 (0.6) | 2 (0.6) | 2 (0.6) |
| Region | n (%) | | | |
| US | | 133 (18.3) | 66 (18.2) | 67 (18.5) |
| Non-US | | 592 (81.7) | 296 (81.8) | 296 (81.5) |
| Height (cm) | | | | |
| | Mean | 175.8 | 176 | 175.5 |
| | SD | 8.02 | 7.84 | 8.2 |
| | Median | 176 | 176 | 176 |
| | Min, Max | 152.0, 206.0 | 152.0, 206.0 | 152.0, 195.0 |
| Weight (kg) | | | | |
| | Mean | 75.5 | 76.9 | 74.1 |
| | SD | 13.49 | 14.39 | 12.38 |
| | Median | 73.8 | 74.5 | 73 |
| | Min, Max | 46.9, 139.9 | 48.0, 139.9 | 46.9, 119.1 |
| BMI (kg/m2) | | | | |
| | Mean | 24.4 | 24.8 | 24 |
| | SD | 3.85 | 4.11 | 3.54 |
| | Median | 23.8 | 24.1 | 23.6 |
| | Min, Max | 15.1, 46.9 | 16.9, 46.9 | 15.1, 36.7 |
| BMI Group | n (%) | | | |
| Underweight (<18.5) | | 18 (2.5) | 9 (2.5) | 9 (2.5) |
| Normal range (18.5 to <25.0) | | 439 (60.6) | 214 (59.1) | 225 (62.0) |
| Overweight (25.0 to <30.0) | | 199 (27.4) | 96 (26.5) | 103 (28.4) |
| Obese (>=30.0) | | 69 (9.5) | 43 (11.9) | 26 (7.2) |

Source: Reviewer's analysis.

**Baseline Characteristics**

The baseline factors were generally balanced between D/C/F/TAF and control groups. Among all randomized patients, 82.2% had baseline HIV-1 RNA ≤ 100,000 copies/mL, 93% had CD4+ cell count ≥ 200 cells/mL, and 84.4% were asymptomatic when they were enrolled in the study. The mean time since patient diagnosed with HIV-1 was 1.6 years (Table 7).

**Table 7: Baseline characteristics, AMBER trial**

| | Statistic | Total (N=725) | D/C/F/TAF (N=362) | Control (N=363) |
|---|---|---|---|---|
| HIV-1 RNA categories (copies/mL) | n (%) | | | |
| <=100,000 | | 596 (82.2) | 303 (83.7) | 293 (80.7) |
| >100,000 | | 129 (17.8) | 59 (16.3) | 70 (19.3) |
| CD4+ cell count (cells/mL) | n (%) | | | |
| <200 | | 51 (7.0) | 22 ( 6.1) | 29 (8.0) |
| >=200 to <350 | | 152 (21.0) | 73 (20.2) | 79 (21.8) |
| >=350 to <=500 | | 235 (32.4) | 114 (31.5) | 121 (33.3) |
| >500 | | 287 (39.6) | 153 (42.3) | 134 (36.9) |
| Time since diagnosis HIV infection (years) | | | | |
| | Mean | 1.6 | 1.6 | 1.6 |
| | SD | 2.79 | 2.5 | 3.06 |
| | Median | 0.4 | 0.5 | 0.4 |
| | Min, Max | 0.1, 25.9 | 0.1, 16.2 | 0.1, 25.9 |
| WHO clinical staging of HIV/AIDS | n (%) | | | |
| Clinical stage 1 (asymptomatic) | | 612 (84.4) | 314 (86.7) | 298 (82.1) |
| Clinical stage 2 (mild symptoms) | | 96 (13.2) | 42 (11.6) | 54 (14.9) |
| Clinical stage 3 (advance symptoms) | | 16 (2.2) | 6 (1.7) | 10 (2.8) |
| Clinical stage 4 (severe symptoms) | | 1 (0.1) | | 1 (0.3) |

Source: Reviewer's analysis.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

About 90% of the patients had treatment adherence >95% at Week 48. No apparent difference in the treatment compliance was observed between D/C/F/TAF and control groups. During the study, no subject used concomitant ARV treatment. The non-ARV concomitant treatment usage between the two groups generally had no difference.

**Efficacy Results – Primary Endpoint**

The difference in the proportion of patients who had HIV-1 RNA <50 copies/mL at Week 48 was 2.7% (D/C/F/TAF group - control group), with lower limit of the 95% CI for the difference larger than the pre-specified NI margin of -10% (Table 8), thus meeting the pre-specified noninferiority margin.

There were missing viral load data for 15 and 30 patients in the D/C/F/TAF group and control group, respectively. Among them, 24 patients discontinued due to AE/death. For those patients, it is reasonable to consider them as virologic failures for both treatment groups, which does not change the efficacy results. However, for the patients who discontinued due to other

reasons (and the last HIV RNA was <50 copies/mL or missing) or just had missing values in the window, a conservative analysis is to consider the outcomes for the 7 patients in the D/C/F/TAF group as failures, and for the 14 patients in the control group as successes. In this case, the difference in the proportion of virologic success changes by -3.9%, with a new lower bound of the 95% CI being approximately -5.55%, which still supports noninferiority.

**Table 8: Proportion of Virologic Response (<50 Copies/mL) According to FDA Snapshot Approach at Week 48, ITT Population, AMBER Trial**

| | | D/C/F/TAF (N=362) | Control (N=363) | Difference in Proportion (95% CI) |
|---|---|---|---|---|
| Virologic success (HIV RNA <50 copies/mL) | | 331 (91.4%) | 321 (88.4%) | 2.7 (-1.65, 7.12) |
| No viral load data in window | | 15 (4.1%) | 30 (8.3%) | |
| | Missing data during window but on study | 3 (0.8%) | 5 (1.4%) | |
| | Discontinued due to other reason and the last available HIV RNA <50 copies/mL (or missing) | 4 (1.1%) | 9 (2.5%) | |
| | Discontinued due to AE/death | 8 (2.2%) | 16 (4.4%) | |
| Virologic failure | | 16 (4.4%) | 12 (3.3%) | |
| | HIV RNA >=50 copies/mL | 9 (2.5%) | 9 (2.5%) | |
| | Virologic failure - discontinued due to other reason and last available HIV RNA >=50 copies/mL | 6 (1.7%) | 3 (0.8%) | |
| | Virologic failure - leading to discontinuation | 1 (0.3%) | | |

Note: Treatment difference and 95% CI were calculated using stratified MH with stratification factors as HIV RNA level (≤100,000 copies/mL or >100,000 copies/mL) and CD4+ cell count (<200 cells/μL or ≥200 cells/μL).
Source: Reviewer's analysis.

**Efficacy Results – Secondary and other relevant endpoints**

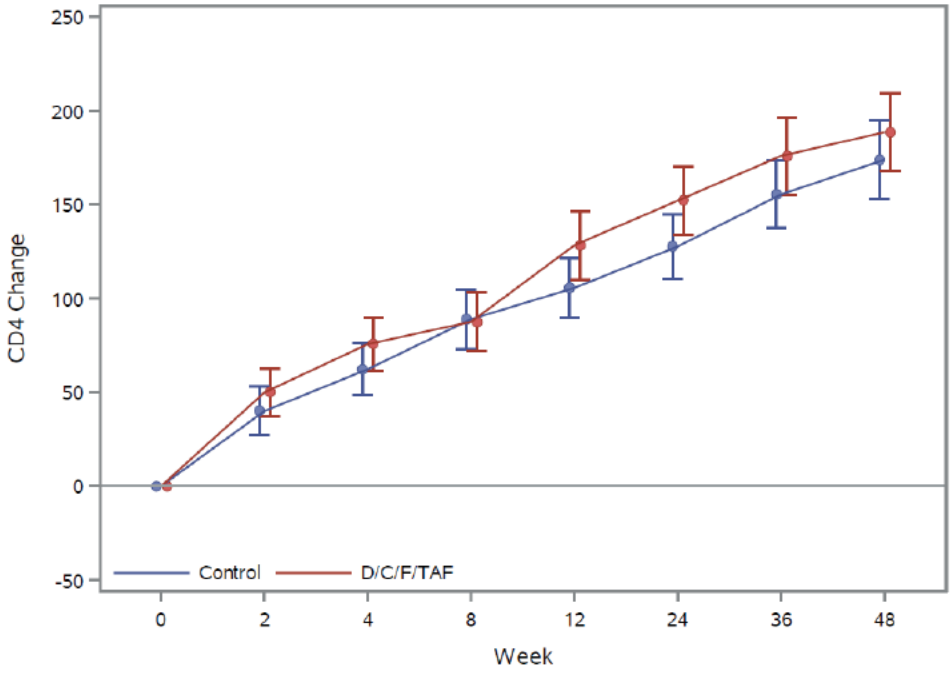
The virologic response rates at Week 48 using cutoff value of 200 copies/mL had similar results compared to the results of using the cutoff value of 50 copies/mL (Table 9). An increase in the mean change from baseline CD4+ cell count was observed for both treatment groups (189 and 174 cells/$mm^3$ in the D/C/F/TAF and control groups, respectively), with no clinically meaningful difference between the two treatment groups (Figure 2). A decrease in the mean change from baseline $log_{10}$HIV-1 RNA was observed right after the treatment drug started for both groups, and reached lowest value around Week 24 (Figure 3).

**Table 9: Proportion of Virologic Response (<200 Copies/mL) According to FDA Snapshot Approach at Week 48, ITT Population, AMBER Trial**

| | D/C/F/TAF (N=362) | Control (N=363) |
|---|---|---|
| Virologic success (HIV RNA <200 copies/mL) | 336 (92.8%) | 329 (90.6%) |
| No viral load data in window | 16 (4.4%) | 30 (8.3%) |
| Virologic failure | 10 (2.8%) | 4 (1.1%) |

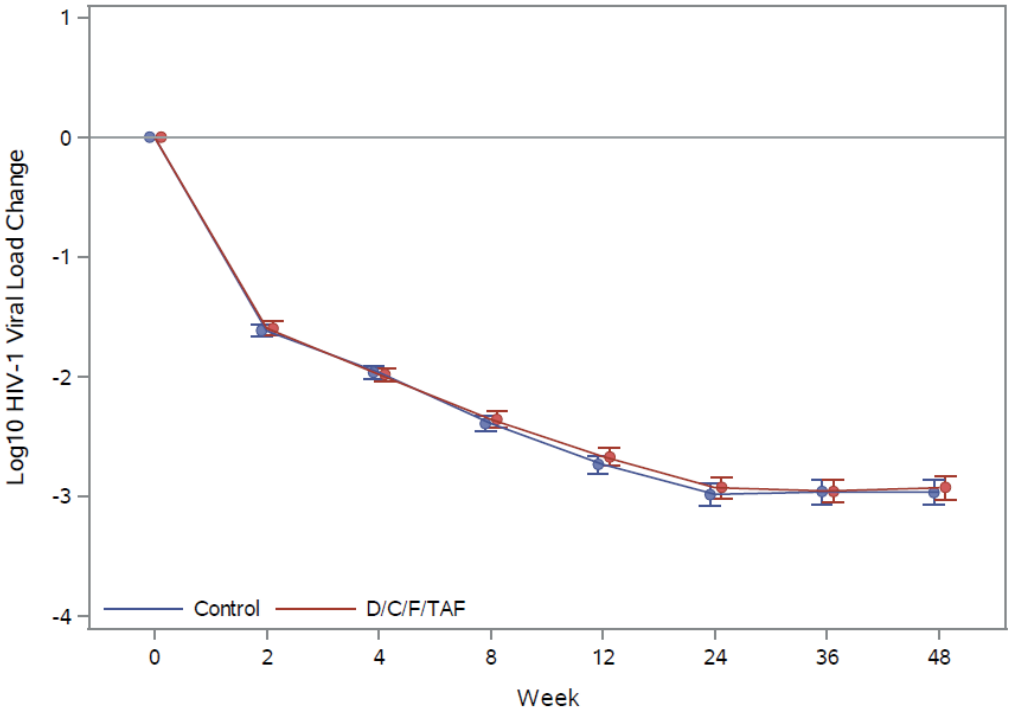
Source: Reviewer's analysis.

**Figure 2: CD4+ Cell Count, Mean Change from Baseline and 95% CI, AMBER Trial**




Source: Reviewer's analysis.

**Figure 3: Log10 HIV-1 RNA, Mean Change from Baseline and 95% CI, AMBER Trial**




Source: Reviewer's analysis.

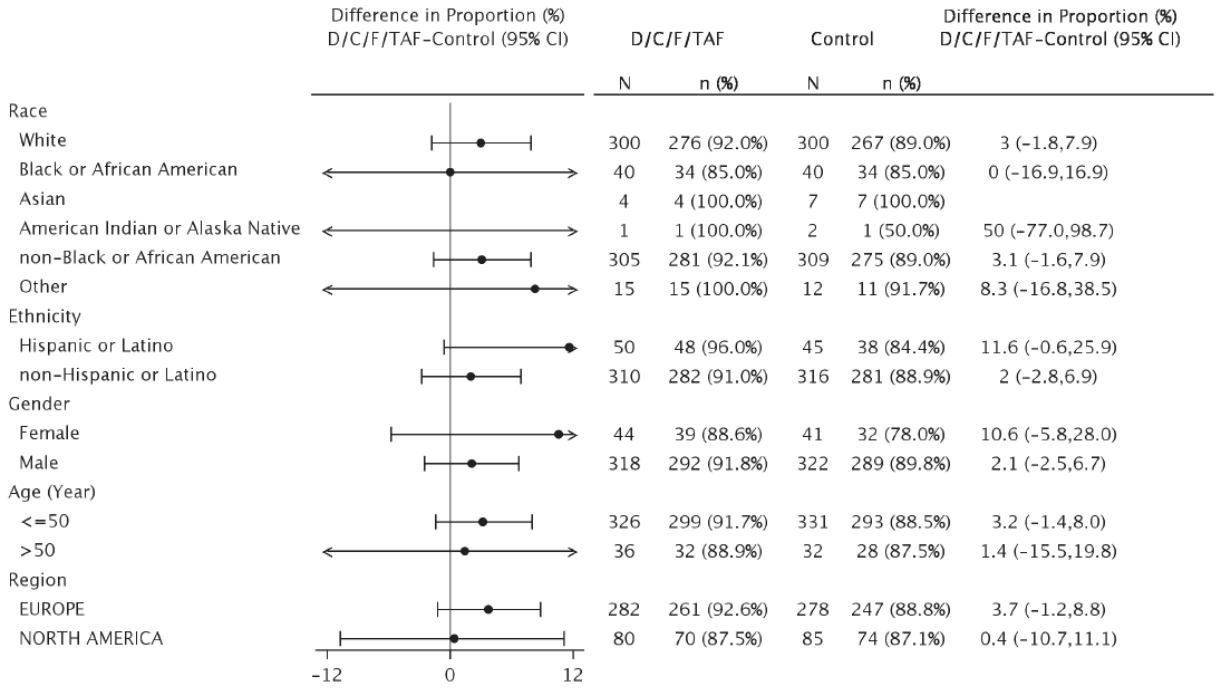
**Findings in Subgroup Populations**

This section summarizes the subgroup results for AMBER. Virologic response (<50 copies/mL) at Week 48 were of main interest of this analysis. All subgroups were assessed within the ITT population.

- **Gender, Race, Age, and Geographic Region**

Results of the virologic response at Week 48 for the demographic subgroups are displayed in Figure 4. In general, the trends were consistent with what had been observed for the overall population. The numeric values of the difference in proportion for all subgroups were generally in the direction that favored D/C/F/TAF treatment.

**Figure 4: Subgroup Analysis in Virologic Response (<50 Copies/mL) at Week 48, Demographic Characteristics, ITT Population, AMBER Trial**

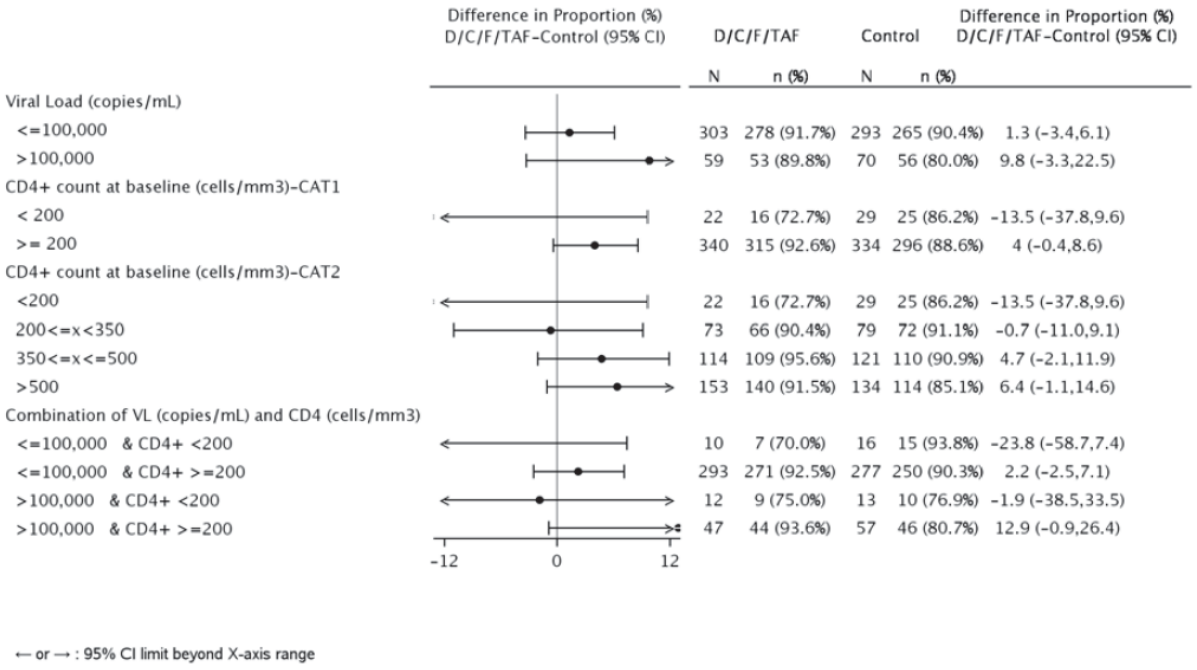



Source: AMBER trial CSR Figure GEFVR14C.

- **Other Special Subgroup Population**

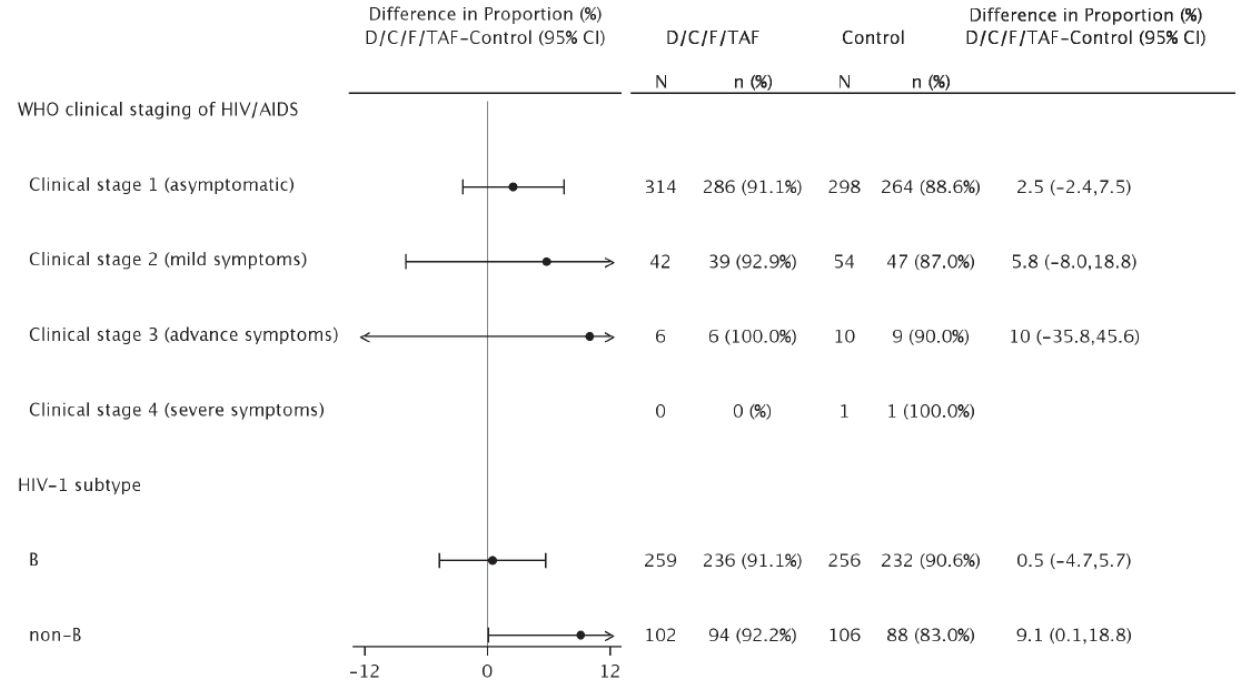
Subgroup analyses were also performed for the randomization stratification factors and baseline disease severity (Figure 5, Figure 6). Small sample sizes for some of the subgroups resulted in wide confidence intervals and associated uncertainties. Several subgroups had difference in proportion favoring the control group, for example, the subgroup with CD4+ cell count < 200 cells/mL. The sample sizes for those subgroups were very small, and thus a couple of more patients responded in one group could flip the result. In general, treatment differences were consistent across subgroups.

**Figure 5: Subgroup Analysis in Virologic Response (<50 Copies/mL) at Week 48, Stratification Factors, ITT Population, AMBER Trial**




Source: AMBER trial CSR Figure GEFVR14A.

**Figure 6: Subgroup Analysis in Virologic Response (<50 Copies/mL) at Week 48, Disease Severity, ITT Population, AMBER Trial**




Source: AMBER trial CSR Figure GEFVR14B.

### 7.2.2. EMERALD Trial

**Trial Design and Endpoints**

EMERALD trial was entitled "A Phase 3, randomized, active-controlled, open-label study to evaluate the efficacy, safety and tolerability of switching to a darunavir/cobicistat/ emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects."

Adult patients with HIV-1 infection and virologically suppressed on a stable ARV regimen for at least 6 months were randomized 2:1 to either switch to a D/C/F/TAF regimen or continue their current regimen (bPI combined with FTC/TDF). Randomization was stratified by bPI used at screening. The primary objective for this study was to demonstrate non-inferiority in efficacy for switching to a D/C/F/TAF once daily single-tablet regimen in terms of the proportion of virologic rebound, which was defined as either having any confirmed HIV-1 RNA ≥50 copies/mL through Week 48, or in case of early discontinuation, a last single viral load of HIV-1 RNA ≥50 copies/mL.

The study included a screening phase, a 48-week treatment phase, followed by another 48-week single arm treatment phase. After Week 96, patients were given opportunity to continue the treatment for an extended period until the drug is commercially available, or the program be terminated by the company (Figure 7).

Study drug was administered as follows:

- D/C/F/TAF Arm: Switch to regimen of an FDC tablet containing DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (further referred to as D/C/F/TAF tablet) once daily, (n = 734); and

- Control Arm: Continue current regimen consisting of a bPI (limited to DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV/rtv) combined with FTC/TDF only, (n = 367).

Virologic responses were evaluated at Week 48. The proposed primary endpoint was the proportion of subjects who had confirmed virologic rebound (HIV-1 RNA ≥ 50 copies/mL) at Week 48, or a last single HIV-1 RNA ≥ 50 copies/mL at early discontinuation. However, the recommended primary endpoint for switch trials is the proportion of patients with HIV RNA ≥50 copies/mL at Week 48 according to the guidance[3]. Secondary endpoints included the

[3] Food Drug Administration, Center for Drugs Evaluation Research (November 2015). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm355128.pdf

proportion of subjects with confirmed virologic rebound through Week 24; Time to virologic rebound in weeks; change from baseline in CD+4 cell count at Week 24 and 48.

**Figure 7: Schematic Overview of EMERALD Trial**

| Baseline (Day 1)[a] | Week 24 | Week 48[b] Primary analysis | Week 96 or beyond[b] |
|---|---|---|---|
| **Screening** | **Treatment phase[c]** | **Extension phase[b,c]** | **Follow-up** |
| **≤30 days prior to baseline** | **Treatment arm 1 (Test)**: D/C/F/TAF once daily[d] (n=734) | D/C/F/TAF[d] | ESTD[c] and/or 30-day FU visit[f] |
| | **Treatment arm 2 (Control)**: Continue current bPI combined with FTC/TDF only[e] (n=367) | | |

[a] Following the baseline visit, subjects will return for study visits at Weeks 2, 4, 8, 12, 24, 36, and 48.

[b] Provided results from the DMC analyses or Week 24 interim analysis does not preclude (further) exposing subjects to D/C/F/TAF, subjects from the D/C/F/TAF arm will enter in the extension phase once they have completed their Week 48 visit. In addition, subjects in the control arm will receive the D/C/F/TAF tablet in the extension phase if, according to the investigator they will benefit from it and if all conditions are fulfilled (which includes adequate viral load results). Subjects from the control arm will be required to attend a switch visit at Week 52 to receive D/C/F/TAF. All subjects in the extension phase will have to attend visits every 12 weeks until Week 96. As from Week 96, all subjects are offered the possibility to continue D/C/F/TAF treatment, if they wish and if they continue to benefit from it, until D/C/F/TAF becomes commercially available and is reimbursed, or can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development. After Week 96, subjects should attend visits every 6 months.

[c] Subjects who prematurely discontinue or change study treatment during the treatment phase (from Day 1 to Week 48) or during the extension phase (only between Week 48 and 96) will be required to complete the ESTD visit assessments within 72 hours of stopping/changing study treatment.

[d] D/C/F/TAF tablet will be administered orally, once daily with food, at approximately the same time each day.

[e] The bPI (DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv) and FTC/TDF should be used in the dosing schedule specified in the ARV agent's local Prescribing Information. Applicable procedures and treatment guidance based on the Prescribing Information should be respected.

[f] Subjects who have an ongoing AE or SAE at the time of their last visit will be required to have a 30-day FU visit (unless consent is withdrawn).

Source: EMERALD trial protocol Figure 1.

**Key Inclusion and Exclusion Criteria**

Patients enrolled in this study were required to meet the following eligibility criteria:

- Having documented HIV-1 infection and currently being treated with a stable ARV regimen consisting of a bPI (limited to DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV/rtv) combined with FTC/TDF only, for at least 6 consecutive months preceding the screening visit.

- Documented evidence of being virologically suppressed while on a stable ARV regimen prior to screening.
- Screening eGFRcr ≥50 mL/min, hepatic transaminases (ALT and AST) ≤5 x upper limit of the normal range (ULN), direct bilirubin ≤1.5 x ULN, and serum amylase ≤2 x ULN.
- Absence of history of failure on DRV treatment and absence of DRV RAMs (including V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V). Note: Absence of history of failure on FTC or TFV treatment and absence of FTC or TFV resistance substitutions were not specified as inclusion criteria.

Key exclusion criteria were:

- Diagnosed with a new AIDS-defining condition within 30 days prior to screening.
- Had proven or suspected acute hepatitis within 30 days prior to screening.
- Hepatitis C antibody positive (however, spontaneously cured hepatitis C virus infection and subjects cured of HCV infection after treatment could participate).
- Hepatitis B surface antigen (HBsAg) positive.
- History of cirrhosis.
- History of malignancy within the past 5 years or ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, resected, noninvasive cutaneous squamous carcinoma, or anal, cervical, or penile intra-epithelial neoplasia.
- Active, severe infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to baseline.
- Any other clinical condition or prior therapy that would make the subject unsuitable for the study or unable to comply with dosing requirements.
- Having drugs not to be used with DRV, COBI, FTC, TAF, and TDF, and could not discontinue them at least 30 days prior to baseline.

**Statistical Analysis Plan**

The primary analysis population was the intent-to-treat (ITT) population, which includes all the subjects who were randomized and received at least 1 dose of study treatment.

The proposed method for the primary analysis was stratum-adjusted Mantel-Haenszel difference of the two treatment arms (D/C/F/TAF –control) in the proportions of patients who had HIV-1 virous rebound. The rebounders were defined as:

- Subjects who show confirmed HIV-1 RNA ≥50 copies/mL up to, and including the upper bound of the Week 48 window (ie, 54 weeks); and

- Subjects who discontinued prematurely (irrespective of reason) for which the last available (single) HIV-1 RNA ≥50 copies/mL.

The stratification factor was bPI use at screen. 95% confidence interval (CI) of the difference in the proportions was calculated using stratified Mantel-Haenszel method. Noninferiority of D/C/F/TAF FDC tablet to control was to be claimed if the upper limit of the 95% CI was less than the pre-specified NI margin of 4%[4].

The planned sample size for EMERALD was 1100 (2:1 randomization) for an 89% power. This was calculated assuming both treatment arms had a rebound rate of 4% at Week 48, with a NI margin of 4% and one-sided significance level of 0.025.

Three interim analyses were conducted. The first interim analysis was for a blinded sample size re-estimation when approximately 50% of subjects reached Week 12 (or prematurely discontinued from the study). It was planned that if the overall Week 48 rebound rate was between 0.04 to 0.06, an increase in sample size by 300 patients would be necessary to maintain the study power at 80%. No sample size increase occurred based on the results of the interim analysis. The second interim analysis was for a formal futility analysis to evaluate the efficacy of D/C/F/TAF regimen using conditional power, when 1149 subjects were enrolled, of which at least 58% reached Week 24 and 0.1% reached Week 48. This analysis was guided by an independent Data Monitoring Committee (DMC), while sponsor and study team remained blinded. The third interim analysis was a formal sponsor-unblinded Week 24 analysis, which happened when all subjects completed 24 weeks of treatment. The main goal was to evaluate the safety and tolerability of the study drug, while efficacy of the 2 treatment arms was also being evaluated.

The efficacy was evaluated at one-sided 0.025 alpha level. Based on the applicant's simulation, blinded sample size re-estimation did not inflate the Type I error much (the maximal increase of Type 1 error was 0.06%), and therefore, no adjustment of p-value was performed to account for the interim analysis.

**Protocol Amendments**

The protocol had four amendments. Substantial changes were made to the amendments regarding the study design, sample size, study objectives, and endpoint, based on FDA recommendations described in Section 3.2. Because those amendments were submitted early during the study, those changes in the protocol were not concerns for data analysis and decision making.

**Patient Disposition**

[4] Food Drug Administration, Center for Drugs Evaluation Research (November 2015). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm355128.pdf

A total of 1141 patients were randomized to the study. The majority of subjects completed 48 weeks of study treatment. The treatment discontinuation rates were similar in the two treatment groups, and the reasons for the pre-mature discontinuation are generally balanced in two groups (Table 10).

**Table 10: Subject Disposition at Week 48, EMERALD Trial**

| | D/C/F/TAF | Control |
|---|---|---|
| Randomized | 763 | 378 |
| Completed study treatment | 729 (95.5%) | 358 (94.7%) |
| Pre-maturely discontinued study treatment | 34 (4.5%) | 20 (5.3%) |
| Adverse event | 11 (1.4%) | 4 (1.1%) |
| Death | | |
| Lost to follow-up | 5 (0.7%) | 5 (1.3%) |
| Non-compliance with study drug | 2 (0.3%) | |
| Physician decision | | |
| Withdrawal by subject | 10 (1.3%) | 8 (2.1%) |
| Other | 6 (0.8%) | 3 (0.8%) |

Source: Reviewer's analysis.

**Protocol Violations/Deviations**

A total of 75 subjects had major protocol deviations (Table 11). No systematic protocol violations or deviations were observed at center level or at study level based on the study report. "Other" protocol deviations were diverse and balanced between groups.

**Table 11: Major Protocol Deviations, EMERALD Trial**

| | D/C/F/TAF | Control | Total |
|---|---|---|---|
| Analysis set: Intent-to-treat, N | 763 | 378 | 1141 |
| Subjects with major protocol deviations | 40 (5.2%) | 35 (9.3%) | 75 (6.6%) |
| Entered but did not satisfy criteria | 13 (1.7%) | 14 (3.7%) | 27 (2.4%) |
| Received wrong treatment or incorrect dose | 4 (0.5%) | 3 (0.8%) | 7 (0.6%) |
| Subject used disallowed medication | 6 (0.8%) | 0 | 6 (0.5%) |
| Other | 20 (2.6%) | 19 (5.0%) | 39 (3.4%) |

Note: Subjects may appear in more than one category

Source: EMERALD trial CSR Table 15.

**Demographic Characteristics**

The majority of randomized subjects were male (82%), white (74.9%), ≤ 50 years of age (66.5%), with non-Hispanic background (84.7%). The number of patients from non-US countries was numerically higher (56.7%). Demographic characteristics were generally balanced between the two treatment groups (Table 12).

**Table 12: Demographic Characteristics, EMERALD Trial**

| | Statistic | Total (N=1141) | D/C/F/TAF (N=763) | Control (N=378) |
|---|---|---|---|---|
| Age (Year) | | | | |
| | Mean | 45.1 | 45.3 | 44.8 |
| | SD | 10.83 | 10.86 | 10.77 |
| | Median | 46 | 46 | 45 |
| | Min, Max | 19.0, 78.0 | 19.0, 75.0 | 20.0, 78.0 |
| Age Group | n (%) | | | |
| <=50 | | 759 (66.5) | 507 (66.4) | 252 (66.7) |
| >50 | | 382 (33.5) | 256 (33.6) | 126 (33.3) |
| Sex | n (%) | | | |
| Male | | 936 (82.0) | 623 (81.7) | 313 (82.8) |
| Female | | 205 (18.0) | 140 (18.3) | 65 (17.2) |
| Race | n (%) | | | |
| White | | 855 (74.9) | 573 (75.1) | 282 (74.6) |
| Black | | 237 (20.8) | 155 (20.3) | 82 (21.7) |
| Asian | | 26 (2.3) | 17 (2.2) | 9 (2.4) |
| Other | | 6 (0.5) | 5 (0.7) | 1 (0.3) |
| Missing | | 8 (0.7) | 6 (0.8) | 2 (0.5) |
| Ethnicity | n (%) | | | |
| Hispanic or Latino | | 170 (14.9) | 111 (14.5) | 59 (15.6) |
| Not Hispanic or Latino | | 966 (84.7) | 649 (85.1) | 317 (83.9) |
| Missing | | 5 (0.4) | 3 (0.4) | 2 (0.5) |
| Region | n (%) | | | |
| US | | 494 (43.3) | 313 (41.0) | 181 (47.9) |
| Non-US | | 647 (56.7) | 450 (59.0) | 197 (52.1) |

| | Statistic | Total (N=1141) | D/C/F/TAF (N=763) | Control (N=378) |
|---|---|---|---|---|
| Height (cm) | | | | |
| | Mean | 174.2 | 174.1 | 174.3 |
| | SD | 9.2 | 9.33 | 8.94 |
| | Median | 175 | 175 | 175 |
| | Min, Max | 144.8, 210.8 | 144.8, 200.7 | 147.0, 210.8 |
| Weight (kg) | | | | |
| | Mean | 79.7 | 80 | 79.2 |
| | SD | 17.17 | 17.34 | 16.83 |
| | Median | 77.3 | 77.8 | 77.1 |
| | Min, Max | 40.5, 204.1 | 40.5, 204.1 | 44.2, 139.8 |
| BMI (kg/m2) | | | | |
| | Mean | 26.2 | 26.4 | 26 |
| | SD | 5.19 | 5.32 | 4.92 |
| | Median | 25.3 | 25.4 | 24.8 |
| | Min, Max | 16.2, 64.6 | 16.4, 64.6 | 16.2, 44.9 |
| BMI Group | n (%) | | | |
| Underweight (<18.5) | | 17 (1.5) | 11 (1.4) | 6 (1.6) |
| Normal range (18.5 to <25.0) | | 526 (46.1) | 339 (44.4) | 187 (49.5) |
| Overweight (25.0 to <30.0) | | 375 (32.9) | 254 (33.3) | 121 (32.0) |
| Obese (>=30.0) | | 222 (19.5) | 158 (20.7) | 64 (16.9) |
| Missing | | 1 (0.1) | 1 (0.1) | |

Source: Reviewer's analysis.

**Baseline Characteristics**

The majority of patients randomized were virologically suppressed at baseline (97.5%), and had CD4+ cell count ≥ 200 cells/mL (98.5%). On average, patients had been diagnosed with HIV-1 infection for about 12 years, and had been taking ARV therapy for 9 years. Boosted DRV was the most prevalent PI used, and the majority of subjects were using rtv as the PI booster (Table 13,

**Table 14**). No relevant differences in the baseline characteristics were observed between the treatment groups.

**Table 13: Baseline Characteristics, EMERALD Trial**

| | Statistic | Total (N=1141) | D/C/F/TAF (N=763) | Control (N=378) |
|---|---|---|---|---|
| HIV-1 RNA categories (copies/mL) | n (%) | | | |
| <50 | | 1113 (97.5) | 744 (97.5) | 369 (97.6) |
| >=50 | | 28 (2.5) | 19 (2.5) | 9 (2.4) |
| CD4+ cell count (cells/mL) | n (%) | | | |
| <200 | | 17 (1.5) | 9 (1.2) | 8 (2.1) |
| >=200 to <350 | | 99 (8.7) | 61 (8.0) | 38 (10.1) |
| >=350 to <=500 | | 229 (20.1) | 157 (20.6) | 72 (19.0) |
| >500 | | 796 (69.8) | 536 (70.2) | 260 (68.8) |
| Time since diagnosis HIV infection (years) | | | | |
| | Mean | 11.6 | 11.8 | 11.3 |
| | SD | 8.36 | 8.44 | 8.18 |
| | Median | 9.3 | 9.3 | 8.9 |
| | Min, Max | 0.6, 35.0 | 0.6, 35.0 | 0.6, 32.6 |
| Time since first ARV therapy (years) | | | | |
| | Mean | 8.7 | 8.8 | 8.5 |
| | SD | 6.71 | 6.82 | 6.5 |
| | Median | 6 | 6.2 | 5.8 |
| | Min, Max | 0.6, 32.9 | 0.6, 32.9 | 0.6, 27.5 |
| WHO clinical staging of HIV/AIDS | n (%) | | | |
| Clinical stage 1 (asymptomatic) | | 777 (68.1) | 522 (68.4) | 255 (67.5) |
| Clinical stage 2 (mild symptoms) | | 147 (12.9) | 96 (12.6) | 51 (13.5) |
| Clinical stage 3 (advance symptoms) | | 102 (8.9) | 66 (8.7) | 36 (9.5) |
| Clinical stage 4 (severe symptoms) | | 115 (10.1) | 79 (10.4) | 36 (9.5) |

Source: Reviewer's analysis.

**Table 14: Boosted PI at Screening, EMERALD Trial**

| | D/C/F/TAF | Control | Total |
|---|---|---|---|
| Analysis set: Intent-to-treat, N | 763 | 378 | 1141 |
| DRV with rtv or COBI | 537 (70.4%) | 266 (70.4%) | 803 (70.4%) |
| DRV with rtv | 439 (57.5%) | 202 (53.4%) | 641 (56.2%) |
| DRV with COBI | 98 (12.8%) | 64 (16.9%) | 162 (14.2%) |
| ATV with rtv or COBI | 167 (21.9%) | 82 (21.7%) | 249 (21.8%) |
| ATV with rtv | 161 (21.1%) | 81 (21.4%) | 242 (21.2%) |
| ATV with COBI | 6 (0.8%) | 1 (0.3%) | 7 (0.6%) |
| LPV with rtv | 59 (7.7%) | 30 (7.9%) | 89 (7.8%) |

Note: Re-classified boosted PI at screening is shown: for the purpose of analysis, the stratification factor (bPI) entered in IWRS at randomization was re-classified based on the value from the history of ARV therapy data at screening.

Source: EMERALD trial CSR Table 9.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Based on the available data (numbers of subjects with data were 215 and 102 for the D/C/F/TAF group and the control group, respectively), about 92% patients had treatment adherence >95% for the D/C/F/TAF group compared to 85% for the control group (Table 15). Considering D/C/F/TAF is a single FDC pill, higher compliance rate reflected the convenience of taking the FDC.

**Table 15: Drug Accountability, EMERALD Trial**

| | D/C/F/TAF | Control | p-value[a] |
|---|---|---|---|
| Analysis set: Intent-to-treat, N | 763 | 378 | |
| Through Week 48 Treatment Adherence, n (%) | | | |
| N | 215 | 102 | 0.091 |
| >95% | 197 (91.6%) | 87 (85.3%) | |
| ]80%; 95%] | 17 (7.9%) | 14 (13.7%) | |
| ]65%; 80%] | 1 (0.5%) | 0 | |
| ≤ 50% | 0 | 1 (1.0%) | |
| Mean (SD) | 99.17 (4.641) | 98.32 (14.595) | |
| Median (Min; Max) | 99.70 (80.0; 134.8) | 99.31 (0.0; 200.0) | |

N: number of subjects with data, n: number of subjects with that observation.
[a] Two-sided p-value from Exact Pearson Chi-Squared test for independence.

Source: EMERALD trial CSR Table 12.

**Efficacy Results – Primary Endpoint**

The applicant proposed to use virologic rebound rate through Week 48 as the primary endpoint. However, there are some concerns associated with this endpoint. Firstly, for the comparable HIV-1 switch treatment trials that were approved, the primary endpoint was the virologic failure rate at Week 48. Consistency of the labeling needs to be maintained. Secondly, for the submitted study, virologic rebound was defined as any confirmed HIV-1 RNA ≥50 copies/mL through the upper bound of the Week 48 window (i.e., 54 weeks). It could be possible that patients who had HIV-1 RNA higher than 50 copies/mL during the early treatment period (because of many reasons such as compliance, fluctuation of HIV-1 RNA levels, etc.) and thus be counted as rebounders had virologic success at Week 48. This was observed by breaking down the virologic rebounders to see the number of successes and failures at Week 48. For the aforementioned reasons and also to follow the guidance, the Agency considers virologic failure rate (HIV-1 RNA ≥50 copies/mL) at Week 48 as the primary endpoint for EMERALD trial. The difference in the proportion of patients who had virologic failure was 0.26% (D/C/F/TAF group - control group), with upper limit of the 95% CI for the difference smaller than the pre-specified NI margin of 4% thus meeting the pre-specified noninferiority margin ( Table 16).

There were missing viral load data for 33 and 22 patients in the D/C/F/TAF group and control group, respectively. Among them, 15 patients discontinued due to AE/death. For the patients in the D/C/F/TAF group who discontinued due to AE/death, it is reasonable to consider them as virologic failures because they had unfavorable outcomes. However, due to the open label study design, patients in the control group may have discontinued due to a relatively minor AE or a desire to switch to a more convenient regimen. Therefore, it is less likely that those patients were virologic failures. Patients who were in the group of discontinued due to other reasons and the last available HIV RNA < 50 copies/mL had viral load suppressed, but still discontinued. For those patients, it is reasonable to consider them as successes for both treatment groups. A conservative analysis is to consider the outcomes for the 14 patients in the D/C/F/TAF group (missing data during window or discontinued due to AE/death) as failures. In this case, the difference in the proportion of patients who had virologic failure changes by 1.8%, with a new upper bound of the 95% CI being approximately 3.02%, which still supports noninferiority.

**Table 16: Proportion of Virologic Failure (≥50 Copies/mL) According to FDA Snapshot Approach at Week 48, ITT Population, EMERALD Trial**

| | D/C/F/TAF (N=763) | Control (N=378) | Difference in Proportion (95% CI) |
|---|---|---|---|
| Virologic failure | 6 (0.8%) | 2 (0.5%) | 0.26 (-0.71, 1.22) |
| HIV RNA >=50 copies/mL | 4 (0.5%) | 2 (0.5%) | |
| Virologic failure - discontinued due to other reason and last available HIV RNA >=50 copies/mL | 2 (0.3%) | | |
| Virologic success (HIV RNA <50 copies/mL) | 724 (94.9%) | 354 (93.7%) | 1.23 (-1.68, 4.14) |
| No viral load data in window | 33 (4.3%) | 22 (5.8%) | |
| Missing data during window but on study | 3 (0.4%) | 2 (0.5%) | |
| Discontinued due to other reason and the last available HIV RNA <50 copies/mL (or missing) | 19 (2.5%) | 16 (4.2%) | |
| Discontinued due to AE/death | 11 (1.4%) | 4 (1.1%) | |
| Virologic rebound **through** Week 48 window (i.e., 54 weeks) | 19 (2.5%) | 8 (2.1%) | 0.37 (-1.45, 2.19) |
| Virologic success (HIV RNA <50 copies/mL) **at** Week 48 | 12 (63.2%) | 4 (50%) | |
| No viral load data in window | 1 (5.3%) | 2 (25%) | |
| Virologic failure | 6 (31.6) | 2 (25%) | |

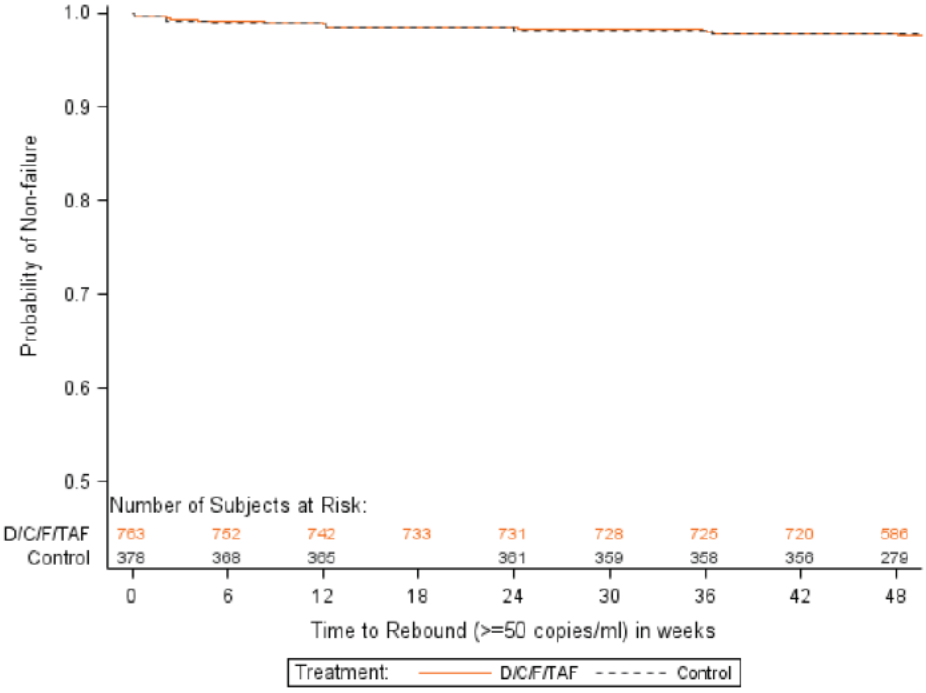
Note: Treatment difference and 95% CI were calculated using stratified MH with stratification factor as bPI use at screening.
Source: Reviewer's analysis.

**Efficacy Results – Secondary and other relevant endpoints**

Through Week 48, there was no difference in time to protocol-defined virologic failure between the two groups (

**Figure 8**). The virologic response rates at Week 48 using the cutoff point of 200 copies/mL had similar results compared to the results of using the cutoff point of 50 copies/mL (Table 17). Compared to the control group, the D/C/F/TAF group had a greater numerical increase in the mean change from baseline CD4+ cell count after Week 4, and this numeric increase became stable from Week 36 to 48. However, the numerical difference between groups is not clinically meaningful. The mean increase from baseline in CD4+ cell count at Week 48 was 20 cells/mm$^3$ patients who switched to D/C/F/TAF and 8 cells/mm$^3$ in patients who stayed on the control regimen (Figure 9).

**Figure 8: Kaplan-Meier Curve of Time to Protocol-defined Virologic Rebound (HIV-1 RNA ≥50 Copies/mL), EMERALD Trial**



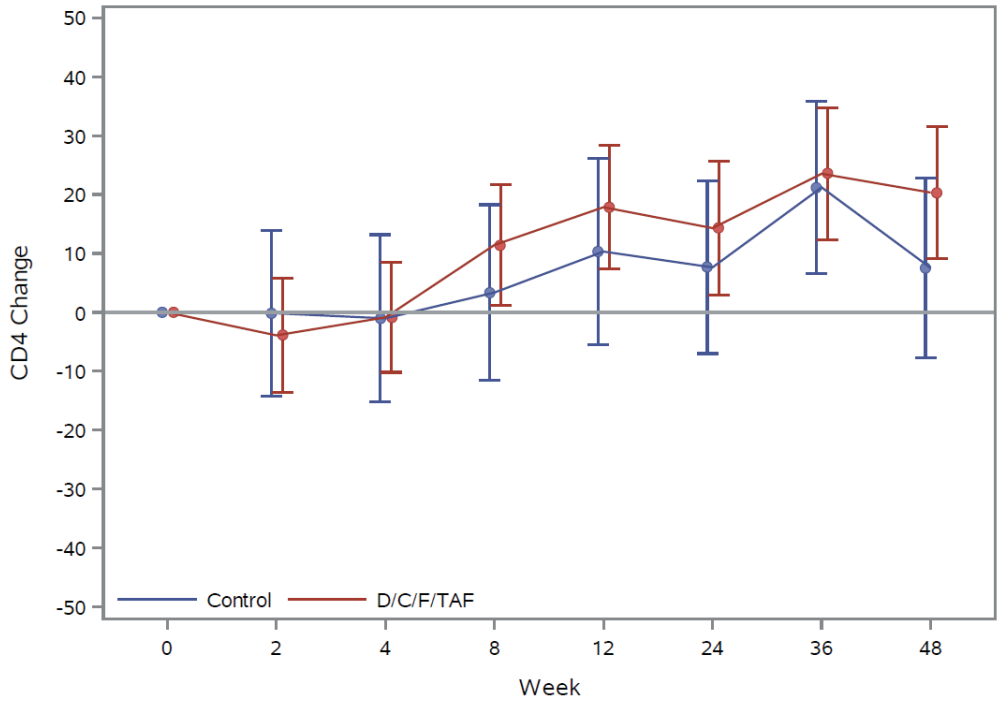

Source: EMERALD trial CSR Figure 5.

**Table 17: Proportion of Virologic Failure (≥200 Copies/mL) According to FDA Snapshot Approach at Week 48, ITT Population, EMERALD Trial**

| | D/C/F/TAF (N=763) | Control (N=378) |
|---|---|---|
| Virologic failure (HIV RNA ≥200 copies/mL) | 3 (0.4%) | 0 |
| Virologic success (HIV RNA <200 copies/mL) | 725 (95%) | 356 (94.2%) |
| No viral load data in window | 35 (4.6%) | 22 (5.8%) |
| Virologic rebound | 3 (0.4%) | 0 |

Source: Reviewer's analysis.

**Figure 9: CD4+ Cell Count, Mean Change from Baseline and 95% CI, EMERALD Trial**




Source: Reviewer's analysis.

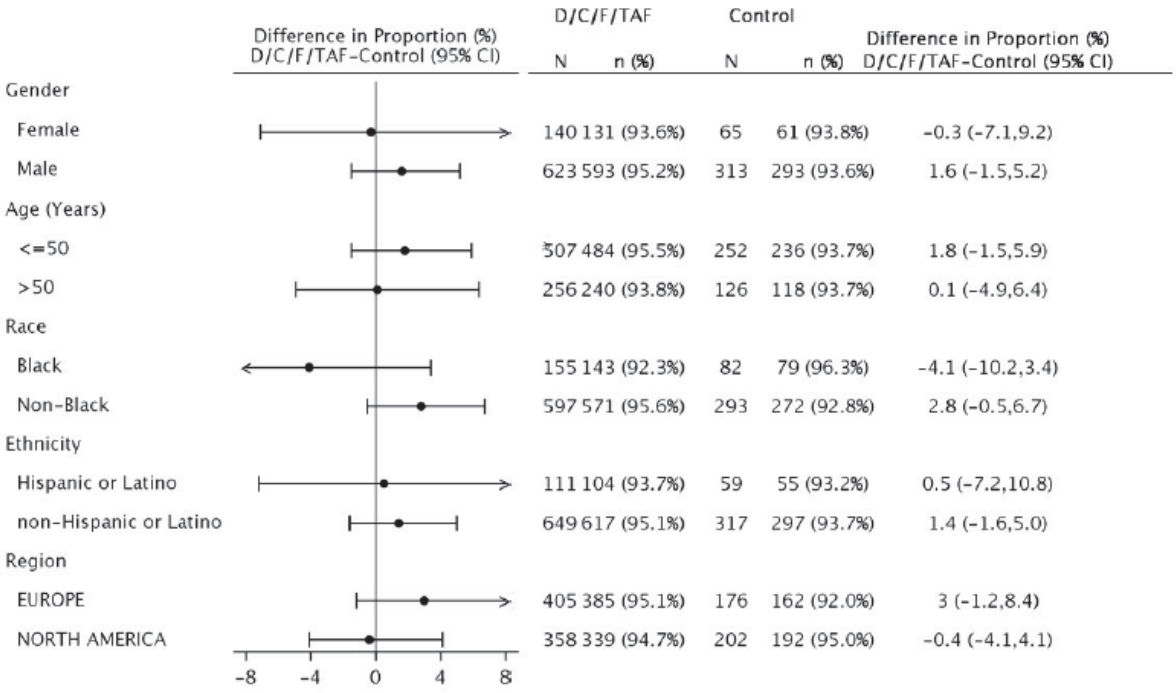
**Findings in Subgroup Populations**

This section summarizes the subgroup results for EMERALD. Virologic response (<50 copies/mL) at Week 48 were of main interest of this analysis, because the virology failure rates were very low and some subgroups did not have any failures in both treatment groups. All subgroups were assessed within the ITT population.

- **Gender, Race, Age, and Geographic Region**

Results of the virologic response at Week 48 for the demographic subgroups are displayed in Figure 10. In general, the trends are consistent with what have been observed for the overall population. There are no concerning patterns in the virologic response rate differences observed for the subgroups.

**Figure 10: Treatment Difference in Virologic Response Rate (<50 Copies/mL) at Week 48, Subgroups by Demographics, Snapshot Algorithm, EMERALD Trial**



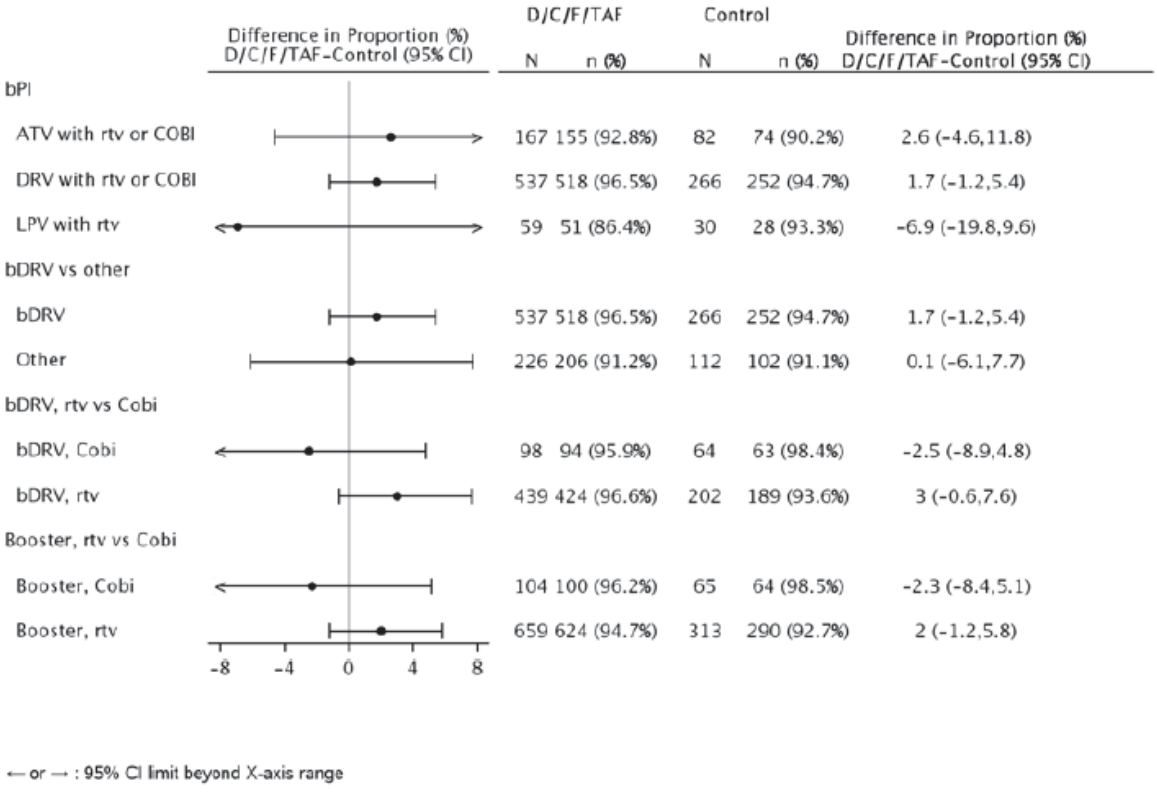

Source: EMERALD trial CSR Figure GEFVR03C.

- **Other Special Subgroup Population**

Subgroup analyses were also conducted for the randomization stratification factors and baseline disease characteristics (Figure 11,

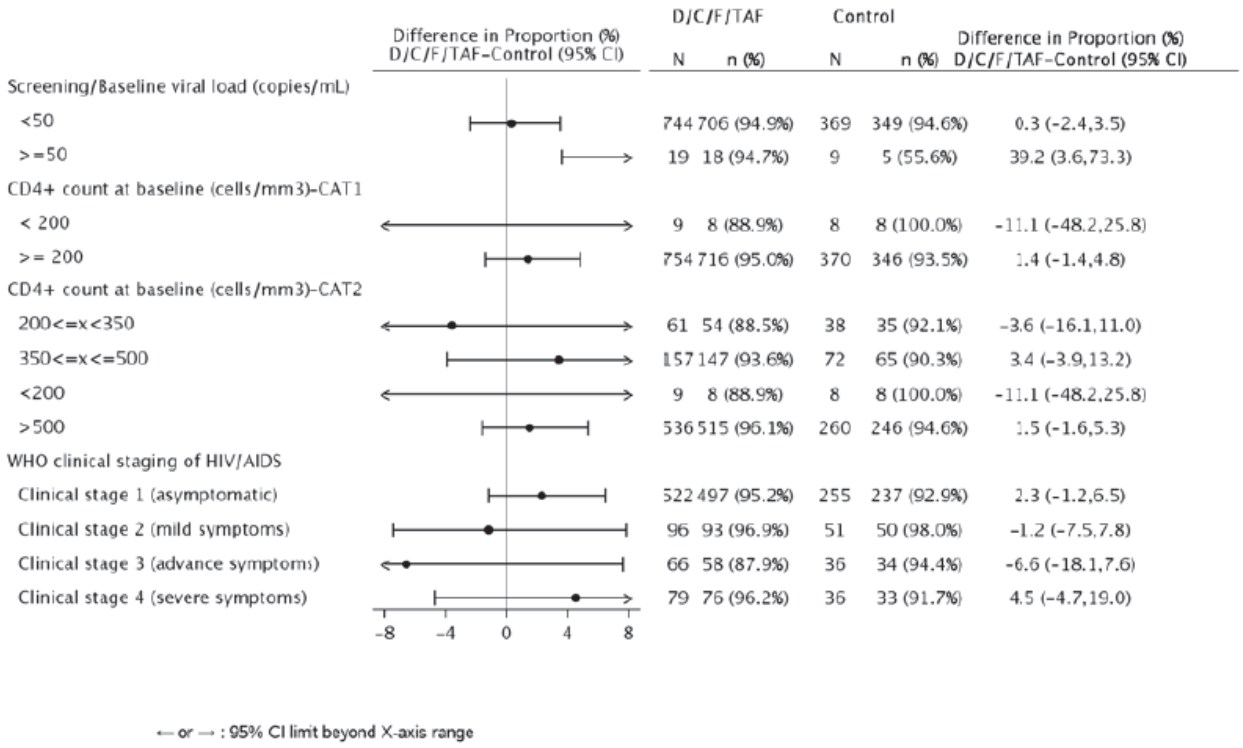
Figure **12**). Small sample sizes for some of the subgroups, resulted in wide confidence intervals. In general, treatment differences were consistent across subgroups.

**Figure 11: Treatment Difference in Virologic Response Rate (<50 Copies/mL) at Week 48, Subgroups by bPI at Screening, Snapshot Algorithm, EMERALD Trial**




Source: EMERALD trial CSR Figure 12.

**Figure 12: Treatment Difference in Virologic Response Rate (<50 Copies/mL) at Week 48, Subgroups by Baseline Characteristics, Snapshot Algorithm, EMERALD Trial**




Source: EMERALD trial CSR Figure 13.

## 7.3. Integrated Review of Effectiveness

### 7.3.1. Assessment of Efficacy Across Trials

**Statistical Issues**

The applicant is seeking approval for the indication of D/C/F/TAF FDC administered once daily in HIV infected treatment naïve patients; and in patients who are HIV infected and virologically suppressed on a stable ARV regimen for at least 6 months. The efficacy evaluation was focused on the two submitted Phase 3 trials, AMBER and EMERALD. The main statistical issues impacting the interpretability of the studies are as follows:

- EMERALD had a formal sponsor-unblinded Week 24 analysis to evaluate the safety and tolerability of the study drug, while also evaluating efficacy. To evaluate whether unblinding the sponsor at Week 24 brought in any bias for the later study conduct, analyses were conducted by this reviewer regarding the Week 24 efficacy. It turned out that the Week 24 result was consistent with the Week 48 result. Therefore, there is no concern for the early unblinding for EMERALD trial. However, for any future study plan, a good practice is to keep the sponsor blinded towards the end of the study so that the

potential bias can be minimized.

**Collective Evidence**

The results of AMBER and EMERALD trials provided adequate statistical evidence for the efficacy of D/C/F/TAF FDC for the following reasons:

- For AMBER, virologic response rates (using HIV-1 RNA 50 copies/mL as threshold) at Week 48 were 91.4% vs 88.4% in the D/C/F/TAF and control group, respectively. The difference in proportion and 95% CI were 2.7% (-1.65% to 7.12%). Lower limit of the 95% CI was above the pre-specified -10% NI margin.

- For EMERALD, virologic failure rates (using HIV-1 RNA 50 copies/mL as threshold) at Week 48 were 0.8% vs 0.5% in the D/C/F/TAF and control group, respectively. The difference in proportion and 95% CI were 0.26% (-0.71% to 1.22%). Upper limit of the 95% CI was below the pre-specified 4% NI margin.

- Results from the subgroup analyses were consistent with the overall results based on the primary endpoint.

## 7.4. Summary and Conclusions

### 7.4.1. Summary and Conclusions

In summary, results from AMBER and EMERALD trials support the conclusion that D/C/F/TAF FDC (800/150/200/10 mg) administered once-daily is non-inferior to the active control in treating HIV-1 infected treatment-naïve or virologic suppressed adult patients, with pre-specified noninferiority margin of -10% (AMBER) or 4% (EMERALD), respectively.

# 8 Clinical Virology Review

## 8.1. Non-Clinical Virology

Please refer to the Virology reviews of NDA-21976 (DRV), NDA-203094 (COBI), NDA-21500 (FTC), NDA-205395 (DRV/COBI), and NDA-207561 (TAF) for complete nonclinical virology reviews of darunavir (DRV), cobicistat (COBI), emtricitabine (FTC), tenofovir alafenamide (TAF).

## 8.2. Clinical Virology

### 8.2.1. Baseline Clinical Virology Resistance: AMBER Trial 3001

The GenoSure MG assay was used for genotypic susceptibility assessments. In the AMBER trial (Trial 3001; in subjects who have no prior antiretroviral treatment history), assessment of screening genotypes showed that the prevalence of PI, NRTI, and NNRTI resistance-associated substitutions at screening was balanced between treatment groups (

**Table 18**). NRTI and NNRTI resistance-associated substitutions were detected in 5% and 16% of the subjects respectively, with K103N being the most prevalent substitution (3%). NNRTI resistance was observed in 10% of the patients at screening based on genotypic susceptibility, mainly due to efavirenz (EFV) and nevirapine (NVP) resistance, which indicate transmitted resistance. At screening, no FTC or TDF/TAF resistance-associated substitutions were detected and all subjects showed 100% susceptibility to DRV, FTC and TFV.

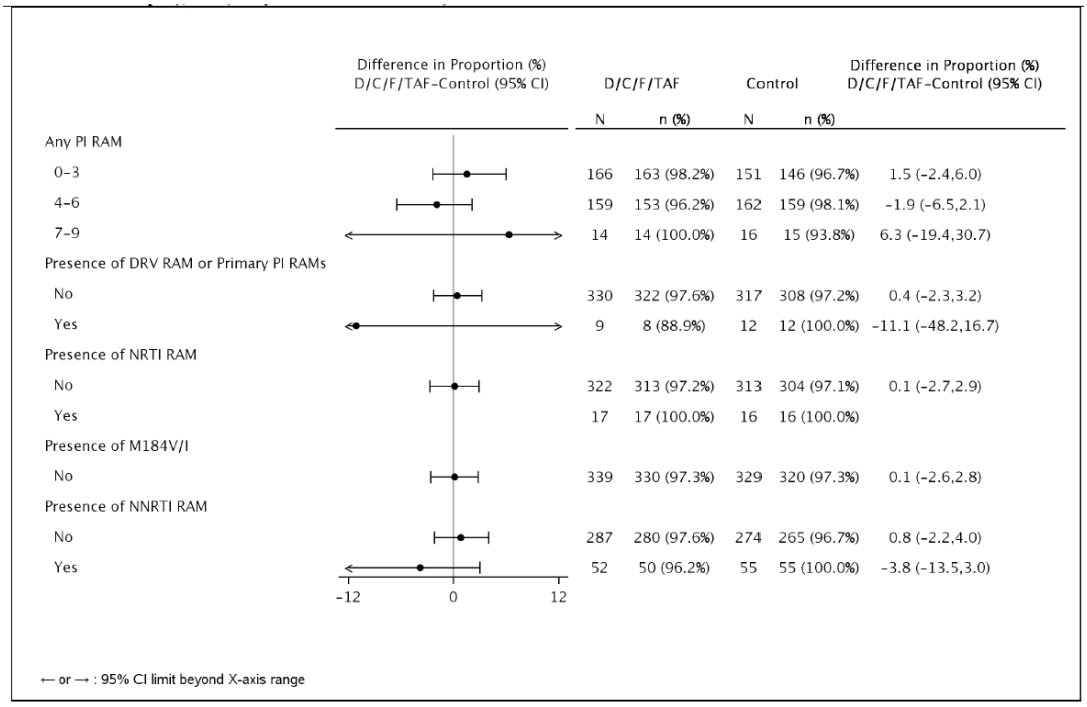
**Table 18. Genotype Susceptibility at Screening in AMBER Trial 3001**

| | D/C/F/TAF | Control | Total |
|---|---|---|---|
| Analysis set: Intent-to-treat, N | 362 | 363 | 725 |
| Subjects with genotype at screening, N | 361 [b] | 362 [b] | 723 |
| Genotypic Susceptibility to, n (%) | | | |
| DRV/rtv | 361 (100.0%) | 362 (100.0%) | 723 (100.0%) |
| FTC | 361 (100.0%) | 362 (100.0%) | 723 (100.0%) |
| TFV | 361 (100.0%) | 362 (100.0%) | 723 (100.0%) |
| All NNRTIs | 327 (90.6%) | 324 (89.5%) | 651 (90.0%) |
| All NRTIs | 353 (97.8%) | 357 (98.6%) | 710 (98.2%) |
| All Pis | 335 (92.8%) | 338 (93.4%) | 673 (93.1%) |
| Subtype, n (%) | | | |
| A | 14 (3.9%) | 10 (2.8%) | 24 (3.3%) |
| A1 | 20 (5.5%) | 33 (9.1%) | 53 (7.3%) |
| AE | 5 (1.4%) | 5 (1.4%) | 10 (1.4%) |
| AG | 19 (5.3%) | 16 (4.4%) | 35 (4.8%) |
| B | 259 (71.7%) | 256 (70.7%) | 515 (71.2%) |
| C | 5 (1.4%) | 11 (3.0%) | 16 (2.2%) |
| COMPLEX [c] | 19 (5.3%) | 22 (6.1%) | 41 (5.7%) |
| Other [d] | 20 (5.5%) | 9 (2.5%) | 29 (4.0%) |

DRV resistance-associated substitutions are defined as V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V.
NRTI resistance-associated substitutions are defined as M41L, A62V, K65R/E/N, D67N, 69ins, K70E/R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215F/Y, and K219E/Q.NNRTI RAMs are defined as V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/S, H221Y, P225H, F227C, and M230I/L.
Primary PI resistance-associated substitutions are defined as D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, and L90M.
Secondary PI substitutions are defined as L10C/F/I/R/V, V11I, G16E, K20I/M/R/T/V, L24I, L33I/F/V, E34Q, M36I/L/V, K43T, F53L/Y, I54A/S/T/V, D60E, I62V, L63P, I64L/M/V, H69K/R, A71I/L/T/V, G73A/C/S/T, V77I, V82I, I85V, N88D, L89I/M/V, and I93L/M.
[Reference: Clinical Study Report TMC114FD2HTX3001, page 97]

The sponsor stated that virologic response rates (<50 HIV-1 RNA copies/mL) at Week 48 were consistent between the treatment groups in any of the subgroups by HIV-1 subtype and baseline resistance factors (HIV-1 subtype (B, non-B), presence of primary PI and/or DRV resistance-associated substitutions, NRTI resistance-associated substitutions, NNRTI resistance-associated substitutions, M184V/I and by primary and secondary PI resistance-associated substitutions. The sponsor's analysis is shown as a forest plot in Figure 13 [source: Clinical Study Report TMC114FD2HTX3001, Attachment GEFVR14E].

**Figure 13. Treatment Difference in Virologic Response (< 50 copies/mL Snapshot Approach) by Resistance-Associated Mutations (RAMs) at Week 48**




**[Source: Clinical Study Report TMC114FD2HTX3001, Attachment GEFVR14E]**

Our analysis examined the effect of DRV substitutions overall, by specific amino acid site and number of DRV resistance-associated substitutions in a censored patient population (removing subjects who discontinued while suppressed (<50 copies/mL)). Efficacy rates were similar in each of these subgroups between the D/C/F/TAF and Control arms (Table 19). We note that some subgroups had small numbers of subjects.

**Table 19. Response by Genotype (Censored Patient Population) (n=704)**

| | D/C/F/TAF | D/C/F/TDF (Control) |
|---|---|---|
| Overall | 94% (335/355) | 93% (324/349) |
| DRV Resistance-Associated Substitutions[1] | 93% (97/104) | 92% (99/108) |
| V11A/I/F | 100% (3/3) | 100% (4/4) |
| L33F/I/V | 88% (7/8) | 100% (17/17) |
| T74A/K/S | 100% (8/8) | 83% (5/6) |
| L89M/I/F | 94% (88/94) | 90% (82/91) |
| 1 DRV RAS | 93% (88/95) | 92% (90/98) |
| 2 DRV RAS | 100% (9/9) | 89% (8/9) |
| Primary PI Substitutions[2] | 93% (27/29) | 91% (20/22) |

Source: FDA Analysis
[1]DRV resistance-associated substitutions are defined as V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V. No subjects had the substitutions V32I, I47V, I50V, I54L/M, L76V, or I84V at screening.
[2]Primary PI resistance-associated substitutions are defined as D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, and L90M.

### 8.2.2. Resistance Analyses of Virologic Failures from AMBER Trial 3001

Post-screening resistance testing was performed on samples from subjects experiencing protocol-defined virologic failure (virologic nonresponse, virologic rebound, and/or viremic at final time point) and who had HIV-1 RNA ≥400 copies/mL at failure or at later time points. At Week 48, 8 subjects in the D/C/F/TAF group ((b) (6) ) and 6 subjects in the control group ((b) (6) ) showed protocol-defined virologic failure, with virologic rebound occurring the most frequently.

Paired screening and post-baseline on-treatment genotypes were available for 7 subjects with protocol-defined virologic failure in the D/C/F/TAF group and 2 in the control group (Table 20). One subject in the D/C/F/TAF group developed a PI resistance-associated substitution I62V. Another subject (PID (b) (6) ) in the D/C/F/TAF group developed M184I/V, conferring resistance to 3TC and FTC. This subject harbored a K103N substitution at screening, indicating transmitted NNRTI (EFV and NVP) resistance. The subject's adherence based on pill count was 102%; however, the observed DRV plasma concentrations for this subject were low (ranging from 32.0 to 192 ng/mL, except at Week 4 [1440 ng/mL]; and much lower than the anticipated DRV steady-state $C_{0h}$ for this subject (~692 ng/mL), which could be an indication that the subject did not take the medication regularly as recommended. The subject was discontinued from the study due to noncompliance after the Week 48 database lock. All other subjects remained susceptible to all the drugs in the treatment regimen based on the genotypic/phenotypic assessments of the (b) (6) .

**Table 20. Virologic Failure Subjects with Post-Baseline Resistance Data from AMBER Trial 3001 (n=9)**

| Patient ID | Arm | Timepoint | Viral Load copies/mL | PI RAS | NNRTI RAS | Phenotype at Failure |
|---|---|---|---|---|---|---|
| (b) (6) | D/C/F/TAF | Week 48 | 11700 | | | Sensitive |
| | D/C/F/TAF | Week 12 | 8810 | L33V<br>M36L | K103N<br>**M184I/V**<br>G196E | DRV 0.68<br>FTC-R 57<br>TAF 0.3 |
| | D/C/F/TAF | Week 12 resuppressed | 2840 | M36I | K101Q | DRV 0.59<br>FTC 1.02<br>TAF 0.91 |
| | D/C/F/TAF | Week 12 | 1260 | M36I<br>I62V<br>V82I | K103N | DRV 0.8<br>FTC 0.99<br>TAF 0.94 |
| | D/C/F/TAF | Week 48 | 4470 | M36I<br>I72V | V118I<br>V189I<br>G196K | DRV 1.14<br>FTC 0.96<br>TAF 0.90 |
| | D/C/F/TAF | Week 36 | 505 | M36I<br>I62V | | DRV 0.72<br>FTC 1.26<br>TAF 0.86 |
| | D/C/F/TAF | Week 48 | 7070 | K20R<br>M36I<br>Q58E<br>**I62V**<br>L89M | T200A | DRV 1.09<br>FTC 1.01<br>TAF 0.82 |
| | | | | | | |
| (b) (6) | D/C/F/TDF | Week 12 DC for AE | 606 | M36I<br>I72**A**/T/**V** | E138A<br>G196Q<br>L210I/M | DRV 1.3<br>FTC 1.5<br>TDF 0.79 |
| | D/C/F/TDF | Week 48 | 173000 | M36I<br>**E65D** | V118I<br>V179A<br>**Q207H**<br>**L210S** | DRV 1.22<br>FTC 0.91<br>TDF 0.61 |

Source: FDA Analysis
PID = Patient Identification Number
RAS = resistance-associated substitution
Emergent substitutions are in bold; emergent resistance-associated substitutions are bolded and underlined.

### 8.2.3. Resistance Analyses of Virologic Failures from EMERALD Trial 3013

In the EMERALD study (Trial 3013; in subjects who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen), there were 6 virologic failures with post-baseline resistance data overall. Of these 6, 4 were rebounders (3 in the control arm and 1 in the D/C/F/TAF arm) (Table 21). Two additional subjects in the D/C/F/TAF arm had no viral load data in the Week 48 window and had genotypes from Week 12 early study discontinuation timepoints. No DRV, primary PI, TFV, or FTC resistance-associated substitutions were observed in these virologic failure subjects and the predicted phenotypic assessment based on GenoSure MG assay showed susceptibility to each of the drugs in the individual treatment regimens. One subject ( (b) (6) ) had an NNRTI resistance-associated substitution E138E/G, conferring resistance to RPV (not related to any of the study drugs). Another subject ( (b) (6) ) had a K103N NNRTI resistance-associated substitution conferring resistance to efavirenz (EFV) and nevirapine, which was probably related to previous Atripla (EFV/FTC/TDF) use.

**Table 21. Virologic Failures with Resistance Data from EMERALD Trial 3013 (n=6)**

| PID | Arm | Timepoint | Viral Load copies/mL | PI RAS | NNRTI RAS | Phenotype at Failure |
|---|---|---|---|---|---|---|
| (b) (6) | Control ATV/r FTDF | Week 8 | 433 resuppressed | I15V M36I | S68G | Sensitive |
| | D/C/F/TAF | Week 12 DC | - | M36I A71T | K103N | EFV-R NVP-R |
| | D/C/F/TAF | Week 12 DC | - | M36I T74S L89M | | Sensitive |
| | Control D/C/F/TDF | Week 8 | 6,390 resuppressed | L10V I15V M36I L89M | E138E/G V179I | RPV-R |
| | D/C/F/TAF | Week 48 | 4,650 | M36I | D67N | Sensitive |
| | Control D/C/F/TDF | Week 24 | 18,400 | T12A G68E A71V V77I I93L | | Sensitive |

Source: FDA Analysis
PID= Patient Identification Number
RAS = resistance-associated substitution

### 8.2.4. Retrospective Analysis of Archived Genotypes

Compared with other recent switch studies, the phase 3 EMERALD study had less strict enrollment criteria for treatment experience: patients with prior experience with multiple

antiretrovirals and/or prior virologic failure, including patients with emtricitabine and tenofovir resistance-associated substitutions, were eligible for study participation. Only an absence of DRV resistance-associated substitutions was required, in case historical genotypes were available. In other switch trials patients could not have any prior virologic failure.

Overall in the EMERALD study, prior to patient's ARV regimen at screening, 664 out of 1,141 (58%) had prior exposure to ARVs and 169 out of 1,141 (15%) patients discontinued prior ARVs due to virologic failure. Prior virologic failure did not impact the efficacy of D/C/F/TAF.

HIV-1 proviral DNA was retrospectively analyzed using the GenoSure Archive® assay (Monogram Biosciences) on baseline samples (HIV-1 RNA <50 copies/mL) from all patients with Protocol Defined Virologic Rebound (N=27) or with prior virologic failure (N=169). Sequence data was obtained for 161 out of these 193 baseline samples. Note that only 3 patients with prior virologic failure had a protocol-defined virologic rebound in this study. In the subgroup of patients with previous virologic failure and genotype archive data (N=140), 5% had TFV resistance-associated substitutions and 38% had FTC resistance-associated substitutions, mainly at reverse transcriptase position M184 (Table 22). In the subgroup of patients with Protocol-defined Virologic Rebound (N=24), none had archived resistance-associated substitutions to FTC and TFV (Table 23). Therefore, archived resistance-associated substitutions to FTC and TFV resistance observed at baseline did not appear to lead to virologic rebound. Thus, the Sponsor proposed to include (b) (4) in the SYMTUZA indication. However, (b) (4) Therefore, the indication excludes virologically suppressed patients with known substitutions associated with resistance to tenofovir and darunavir. (b) (4) .

**Table 22. Prevalence of Resistance-Associated Substitutions at Baseline for Subjects with Previous Virologic Failure**

| | D/C/F/TAF | Control | Total |
|---|---|---|---|
| Analysis set: Intent-to-treat, N | 763 | 378 | 1141 |
| Subjects with previous virologic failure, N | 116 | 53 | 169 |
| Subjects with previous virologic failure and geno archive data at baseline, N | 98 | 42 | 140 |
| **TFV RAMs**[a] , n(%) | | | |
| K65K/R | 2 (2%) | 0 | 2 (1.4%) |
| K65R | 2 (2%) | 0 | 2 (1.4%) |
| K70E/Q | 1 (1%) | 0 | 1 (0.7%) |
| K70K/D/E/N | 0 | 1 (2.4%) | 1 (0.7%) |
| K70K/E | 1 (1%) | 0 | 1 (0.7%) |
| **TFV RAMs**, n(%) | | | |
| 1 | 6 (6.1%) | 1 (2.4%) | 7 (5%) |
| **FTC RAMs**[a] , n(%) | | | |
| K65K/R | 2 (2%) | 0 | 2 (1.4%) |
| K65R | 2 (2%) | 0 | 2 (1.4%) |
| M184M/I | 1 (1%) | 1 (2.4%) | 2 (1.4%) |
| M184M/I/V | 1 (1%) | 1 (2.4%) | 2 (1.4%) |
| M184M/V | 29 (29.6%) | 12 (28.6%) | 41 (29.3%) |
| M184V | 0 | 4 (9.5%) | 4 (2.9%) |
| **FTC RAMs**, n(%) | | | |
| 1 | 34 (34.7%) | 17 (40.5%) | 51 (36.4%) |
| 2 | 1 (1%) | 1 (2.4%) | 2 (1.4%) |

The denominator is subjects with previous virologic failure and geno archive data at baseline.
[a] IAS-USA 2017 mutation list
[TVIRES02.RTF] [/SAS/3027/TMC114IFD3013/FILES/RE/ABSTRACT_GENOARCHIVE_WK48/MACROS/TVIRES02.SAS] 21MAR2018, 12:43

Source: Response to FDA Advice Information Request SDN017, 13 April 2018, page 6

**Table 23. Prevalence of Resistance-Associated Substitutions at Baseline for Subjects with Protocol-Defined Virologic Rebound**

| | D/C/F/TAF | Control | Total |
|---|---|---|---|
| Analysis set: Intent-to-treat, N | 763 | 378 | 1141 |
| Subjects with Protocol-defined Virologic Rebound, N | 19 | 8 | 27 |
| Subjects with Protocol-defined Virologic Rebound and geno archive data at baseline, N | 17 | 7 | 24 |
| ≥1 TFV RAMs[a] , n(%) | 0 | 0 | 0 |
| ≥1 FTC RAMs[a] , n(%) | 0 | 0 | 0 |

[a] IAS-USA 2017 mutation list
[TVIRES03.RTF] [/SAS/3027/TMC114IFD3013/FILES/RE/ABSTRACT_GENOARCHIVE_WK48/MACROS/TVIRES03.SAS] 21MAR2018, 12:43

Source: Response to FDA Advice Information Request SDN017, 13 April 2018, page 7

### 8.2.5. Conclusion

In the AMBER study of ARV treatment-naïve HIV-1-infected adult subjects, NRTI and NNRTI resistance-associated substitutions were detected at screening in 5% and 16% of the subjects respectively, with K103N being the most prevalent substitution (3%). NNRTI resistance was observed in 10% of the patients at screening based on genotypic susceptibility. No FTC or TDF/TAF resistance-associated substitutions were detected at screening and all subjects showed 100% susceptibility to DRV, FTC and TFV.

Efficacy rates were similar between the D/C/F/TAF and D/C/F/TDF arms in subgroups of specific amino acid sites associated with DRV resistance and number of DRV resistance-associated substitutions in a censored patient population removing subjects who discontinued while suppressed (<50 copies/mL). At Week 48, 8 subjects in the D/C/F/TAF group and 6 subjects in the control group showed protocol-defined virologic failure, with virologic rebound occurring the most frequently. Screening and post-baseline on-treatment genotypes were available for 7 of the failure subjects in the D/C/F/TAF group and 2 in the control group. One subject in the D/C/F/TAF group who was discontinued due to noncompliance developed M184I/V, conferring resistance to 3TC and FTC. This subject harbored a K103N substitution at screening, indicating transmitted NNRTI (EFV and NVP) resistance.

In the EMERALD study, there were 6 virologic failures with post-baseline resistance data overall. Of these 6, 4 were rebounders (3 in the control arm and 1 in the D/C/F/TAF arm). Two additional subjects in the D/C/F/TAF arm had no viral load data in the Week 48 window and had Week 12 Early study discontinuation genotypes. No DRV, primary PI, TFV, or FTC resistance-associated substitutions were observed in these virologic failure subjects and all these subjects were susceptible to each of the drugs in the individual treatment regimens.

From a virology perspective, approval of D/C/F/TAF as a complete regimen for the treatment of HIV-1 infection in adults who have no prior antiretroviral treatment history or who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir is fully supported. The FDA-negotiated labeling for Section 12.4 "Resistance *Clinical Trials*" in the drug package insert is shown below:

*In the AMBER clinical trial of subjects with no prior antiretroviral treatment history, there were 7 subjects with protocol-defined virologic failure and with HIV-1 RNA ≥400 copies/mL at failure or later timepoints who had post-baseline resistance data in the SYMTUZA arm. None of the subjects had detectable emergent darunavir resistance-associated substitutions or other primary protease inhibitor resistance substitutions and only one subject had emergent M184M/I/V, which confers resistance to emtricitabine and lamivudine. In the comparative PREZCOBIX + emtricitabine/tenofovir disoproxil fumarate arm, there were 2 protocol-defined virologic failures with post-baseline resistance data and neither had detectable resistance emergence.*

*In the EMERALD clinical trial of virologically-suppressed subjects who switched to SYMTUZA, 1 subject who rebounded and 2 subjects who discontinued early from the study had post-baseline resistance genotypes. None of the subjects had darunavir, primary protease inhibitor, emtricitabine, or tenofovir resistance substitutions. In the control arm, there were 3 subjects who rebounded with post-baseline genotypes and no resistance substitutions were observed.*

# 9 Review of Safety

## 9.1. Safety Review Approach

The sources of data for the safety review are the Phase 3 trials, AMBER and EMERALD. Both trials were analyzed individually, rather than pooled, for all safety analyses because of differences in study design and population. Using the Applicant's SDTM and ADaM datasets, all safety analyses presented in this section were conducted by the FDA reviewer, unless otherwise specified, using MAED, JReview 11.0, and/or JMP Clinical 6.0.

In this review, clinical and laboratory AEs are combined for deaths, serious adverse events (SAEs), and discontinuations due to adverse events (AEs), and separated for other safety results as noted in each subsection. Because the Applicant combined clinical and laboratory AEs for all safety results, the numerical findings in some sections of this review differ slightly from the Applicant's report. The rationale for separating clinical and laboratory AEs is that not all investigators report laboratory abnormalities as an AE, and separate analyses of laboratory values uniformly capture abnormalities. Note: the method for excluding laboratory abnormalities from certain analyses was by exclusion of the SOC Investigations; this method was imperfect because some laboratory AEs, such as hypercholesterolemia, reside within a different SOC. These discrepancies are addressed throughout the review. Overall, the findings are still generally consistent with those of the Applicant.

Of note, the main comparison in the treatment-naïve population is TAF versus TDF because DRV/c and FTC are components of the regimen in each group. However, the AMBER trial provides the first 48-week randomized controlled trial data with DRV/c. Therefore, the safety analysis in this review focuses not only on the D/C/F/TAF group but also the comparator group, D/C/F/TDF. Both groups in the AMBER trial provide a safety perspective on DRV/c and are indirectly compared to prior clinical trials with DRV/r.

The Applicant submitted a Safety Update Report (SUR) four months after the original NDA submission. No new safety concerns were identified in the SUR based on a review of deaths and SAEs and thus, the details are not discussed in this review. Please refer to the Applicant's SUR for details.

## 9.2. Review of the Safety Database

### 9.2.1. Overall Exposure

Table 24 describes the overall number of individuals exposed to D/C/F/TAF in this development program. Because all four components are approved products, the total exposure of each component administered together or separately from current and prior clinical trial experience is actually higher than shown.

**Table 24. Clinical Trial Safety Database: Population and Size**

| Clinical Trial Groups | D/C/F/TAF (n=1491) | Active Control (n=1007) |
|---|---|---|
| Phase 1 trials in HIV-negative participants | N=263 | N=216 |
| Phase 2 trials in HIV-infected participants | N=103 | N=50 |
| Phase 3 trials in HIV-infected participants (AMBER and EMERALD) | N=1125 | N=741 |

*Source: Applicant's Summary of Clinical Safety, Table 3*

#### 9.2.2. Relevant characteristics of the safety population

The safety population is the same as the ITT (randomized) populations used in the efficacy analysis for both trials. See Table 6 and Table 12 for details.

#### 9.2.3. Adequacy of the safety database

The safety database from the AMBER and EMERALD trials includes more than 500 HIV-infected patients who received the proposed dose for at least 48 weeks, which is consistent with the recommendations in the Guidance to Industry for HIV-1 Infection: Developing Antiretroviral Drugs for Treatment. Thus, the safety data submitted are adequate to characterize the safety profile of D/C/F/TAF in treatment-naïve and virologically suppressed HIV-infected patients.

### 9.3. Adequacy of Applicant's Clinical Safety Assessments

#### 9.3.1. Issues Regarding Data Integrity and Submission Quality

Data integrity appears generally adequate based on:

- Comparison of verbatim reported terms to MedDRA preferred terms (PTs)
- Comparison of narratives for deaths, SAEs, treatment discontinuations, and selected AEs of interest to the Applicant's summary and assessment

The comparisons did not yield any major quality or integrity issues that would preclude a comprehensive safety review.

#### 9.3.2. Categorization of Adverse Events

For the AMBER and EMERALD trials, the Applicant used the Division of AIDS (DAIDS) grading table (version 2.0, November 2014).

The term AE indicates the event occurred irrespective of causality, while adverse drug reaction

(ADR) indicates the AE was deemed possibly, probably, or very likely related to study drug by the investigator. All AEs and ADRs discussed in this review were treatment-emergent, unless otherwise noted. Treatment-emergent indicates the AE or ADR newly appeared after starting study treatment or worsened if already present at baseline and occurred either while on treatment (through the Week 48 window) or during the follow-up period (72 hours) after early discontinuation.

#### 9.3.3. Routine Clinical Tests

Routine clinical evaluation and laboratory testing occurred at prespecified regular intervals consistent with standard-of-care for the patient population and/or based on standard clinical trial design for the population and indication. The frequency and scope of testing were adequate based on the standards as well as prior clinical trial experience with the individual components.

### 9.4. Safety Results

#### 9.4.1. Overview

Table 25 presents a high-level safety overview for the AMBER and EMERALD trials. Differences of at least 5% between groups are highlighted in gray. Of note in the EMERALD trial, the difference in the rate of drug-related clinical AEs is not unexpected because the baseline PI (bPI) group continued a stable regimen, whereas the D/C/F/TAF group initiated a new regimen, and the trial was not blinded. See subsections below for additional details and assessment.

**Table 25. Overview of Treatment-Emergent Adverse Events in Phase 3 Safety Population in the AMBER and EMERALD trials through Week 48**

| Participants Experiencing Event N (%) | AMBER Trial | | EMERALD Trial | |
|---|---|---|---|---|
| | D/C/F/TAF N=362 | D/C/F/TDF N=363 | D/C/F/TAF N=763 | bPI n=311 |
| Serious Adverse Event (SAE) | 17 (5) | 21 (6) | 35 (5) | 18 (5) |
| Fatal Outcome | 0 | 1 (<1) | 0 | 0 |
| Drug Related | 0 | 6 (2) | 1 (<1) | 0 |
| AE Leading to Discontinuation of Study Drug | 8 (2) | 16 (4) | 11 (1) | 4 (1) |
| Any Clinical AE[1] | 310 (86) | 305 (84) | 618 (81) | 307 (81) |
| Grade 3 or 4 | 13 (4) | 20 (6) | 37 (5) | 25 (7) |
| Drug-Related Clinical AE[1,2] | 116 (32) | 145 (40) | 128 (17) | 21 (6) |
| Grade 3 or 4 | 3 (1) | 5 (1) | 3 (<1) | 3 (1) |

*Source: FDA Analysis, JReview 11.0, ADAE and ADSL datasets*
[1]Clinical AE excludes events within the SOC Investigations
[2]Relatedness assessed by the investigator

### 9.4.2. **Deaths**

AMBER Trial

No deaths occurred in the D/C/F/TAF group.

One death (USUBJID (b) (6) ) occurred in the D/C/F/TDF group on Day 158, 11 days after discontinuing study drug due to grade 4 sclerosing cholangitis. The cause of death was reported as sepsis of unknown origin along with multi-organ failure and was deemed not related to study drug. An autopsy was not performed. The investigator's assessment is reasonable.

EMERALD Trial: No deaths occurred in either group.

### 9.4.3. **Serious Adverse Events**

AMBER Trial

SAEs of any grade occurred at a similar rate in both arms (5-6%). Overall differences between treatment groups include:

- D/C/F/TAF: none were related to study drug per investigator; one resulted in discontinuation of study drug
- D/C/F/TDF: six were related to study drug per investigator; eight resulted in discontinuation of study drug

The SOC with the largest imbalance between groups was Skin and Subcutaneous Disorders: 0/362 and 5/363 (1%) with D/C/F/TAF and D/C/F/TDF, respectively. All five skin-related SAEs in the D/C/F/TDF group were deemed related to study drug, and four led to permanent discontinuation of D/C/F/TDF. PTs included Stevens-Johnson syndrome (SJS) (1), toxic skin eruption (2), and rash (2). Based on a review of these narratives, causality assessment by Investigators and rationale for discontinuation were appropriate. The events are consistent with the known safety profile of DRV. See Section 9.5.1 for additional analysis of skin reactions.

The SOC with the highest rate of reported events across groups was Infections and Infestations: 6/362 (2%) and 5/363 (1%). Based on a review of the narratives, no new safety signals were identified. Causality assessments by investigators as "not related" for all events were reasonable, as the events were likely due to underlying HIV infection, pre-existing condition, or background rate.

Three SAEs of suicidal ideation or suicide attempt (1 in the D/C/F/TAF group and 2 in the D/C/F/TDF group) occurred in participants with underlying depression and/or history of suicidal ideation and/or were associated with a precipitating event. These terms are not in the current labels for DRV- or TAF-containing products or in the proposed label for D/C/F/TAF, which is

reasonable at this time based on narrative review.

Overall, no new safety signals or trends were identified through analysis of SAEs, including narrative review. The imbalance of SAEs deemed related to study drug and/or resulting in discontinuation of study drug with D/C/F/TDF did not raise any new safety concerns.

EMERALD Trial

SAEs occurred at a similar rate between treatment groups and at a similar rate compared to the AMBER trial (Table 25). No new safety concerns arose that warrant additional labeling.

Of note, one SAE was possibly related per the investigator. USUBJID (b) (6) experienced pancreatitis approximately 5 months after switching from DRV/r and F/TDF to D/C/F/TAF. CT results revealed pancreatitis Balthazar D; no pancreatic necrosis; and no organic reason for pancreatitis. The participant had no known history of pancreatitis or gallstones. One confounding factor was moderate alcohol consumption. The investigator assessed causality of study drug as possibly related because of temporal relationship and lack of alternative factors. The participant was restarted on a nucleos(t)ide-sparing regimen of raltegravir and etravirine.

*Reviewer Comment: The Investigator's assessment is reasonable, and pancreatitis is included in the TAF (Vemlidy) label. Of note, no other participant experienced pancreatitis (any cause, any severity) across both trials. The Applicant's proposed labeling for pancreatitis in Section 6.1 Less Frequent Adverse Reactions is reasonable.*

### 9.4.4. Dropouts and/or Discontinuations Due to Adverse Effects

AMBER Trial

The rate of discontinuations due to AE was lower in the D/C/F/TAF group versus the D/C/F/TDF group (Table 26).

**Table 26. Discontinuations due to AE in the AMBER trial through Week 48**

| Participants Experiencing Event, N (%) | D/C/F/TAF N=362 | D/C/F/TDF N=363 |
|---|---|---|
| AE Leading to Discontinuation of Study Drug | 8 (2)[1] | 16 (4)[2] |
| Skin and Subcutaneous Tissue Disorders | | |
| Serious Skin Reaction | 0 | 4 |
| Non-serious, Grade 2 Rash Event | 6 | 6 |
| Diarrhea | 1 | 1 |

*Source: FDA Analysis, JReview 11.0, ADAE and ADSL datasets*
[1]Additional AE leading to discontinuation of D/C/F/TAF: thrombosis
[2] Additional AE leading to discontinuation of D/C/F/TDF: arthralgia, beta2 microglobulin increased, bone marrow edema, squamous cell carcinoma of lung, sepsis/cholangitis sclerosing

Skin and subcutaneous tissue disorders were responsible for most discontinuations due to AE (Table 26). Four of the ten skin-related events with D/C/F/TDF leading to treatment discontinuation were serious (see Section 9.4.3). Excluding serious skin reactions, an equal percentage of participants in each group discontinued due to a rash event. The narratives for these events were similar in nature and severity and consistent with the known profile of DRV. See Section 9.5.1 for comprehensive analysis of skin reactions.

The narratives for both discontinuations due to diarrhea are consistent with the known safety profile of DRV, and diarrhea is included in the proposed D/C/F/TAF label.

Overall, no new safety signals or trends were identified through analysis of discontinuations due to AE, including narrative review. The imbalance between groups is partially explained by the higher rate of discontinuation due to skin reactions with D/C/F/TDF but not by any other specific safety issue.

EMERALD Trial

Discontinuations due to AE occurred at a similar rate between treatment groups and at a lower rate compared to the AMBER trial (Table 25). The lower rate is not unexpected because participants were already receiving either similar or the same antiretroviral treatment at baseline (70% of baseline regimens included DRV/r or DRV/c). The most common AEs leading to discontinuation were gastrointestinal disorders (diarrhea, abdominal pain, and/or GERD) or kidney disorders (renal tubular disorder, nephropathy toxic, or chronic kidney disease). These events are not unexpected and are adequately labeled. Overall, no new safety signals were identified.

### 9.4.5. **Significant Adverse Events**

The DAIDS grading table categorizes severe events as Grade 3 and potentially life-threatening events as Grade 4. This section includes analysis of Grade 3 and 4 clinical AEs.

AMBER Trial

Grade 4 AEs occurred in 0/363 and 5/363 (1%) participants in the D/C/F/TAF and D/C/F/TDF groups, respectively. All Grade 4 AEs were serious, and one was fatal (see Sections 9.4.2 and 9.4.3, respectively).

Grade 3 AEs occurred at a similar rate in both groups: 13/362 (4%) and 17/363 (5%) with D/C/F/TAF and D/C/F/TDF, respectively. Approximately 1% of Grade 3 AEs in each group were at least possibly related to study treatment per investigator. No clinical AEs occurred in more than one participant; hypercholesterolemia occurred in two participants in the D/C/F/TAF group (see Section 9.4.7), but this event was a laboratory-based event (not excluded in this

analysis because it does not reside within the Investigations SOC). Overall, no new safety signals were identified.

EMERALD Trial

The findings in this trial were similar to the findings in the AMBER trial. No new safety signals were identified.

### 9.4.6. Treatment Emergent Adverse Events and Adverse Reactions

AMBER Trial

Most participants in both groups experienced at least one clinical AE, but less than half were assessed as related to study treatment by investigators (Table 25). In the D/C/F/TAF group, 68% (79/116) and 29% (34/116) of ADRs were Grade 1 and Grade 2, respectively, and the D/C/F/TDF group was similar. Of the Grade 3 ADRs, only one event of liver injury in the D/C/F/TAF group was a true clinical ADR; the other Grade 3 ADRs were laboratory-driven events (e.g., hypercholesterolemia) but not excluded because it does not reside in the Investigations SOC.

The SOC containing the most ADRs in both groups and the largest discrepancy between groups was Gastrointestinal disorders: 64 (18%) and 82 (23%) with D/C/F/TAF and D/C/F/TDF, respectively. Most gastrointestinal ADRs in both groups (87-88%) were mild intensity, and none were severe. The most common gastrointestinal ADRs were diarrhea, nausea, abdominal discomfort/distension/ pain, and flatulence.

Table 27 and Table 28 display ADRs by PT, all Grades and ≥ Grade 2, respectively, that occurred in at least 2% of participants in either group. The between-group differences for clinical ADRs such as diarrhea, nausea, headache, and fatigue are consistent with prior TAF versus TDF comparisons (e.g., E/C/F/TAF versus E/C/F/TDF). Similar PTs for rash, fatigue, and abdominal pain/discomfort were combined to minimize dilution of a potential signal. The pooled rash terms are generally consistent with the pooled terms in the Tybost (cobicistat) label and vary slightly from the Applicant's pooled terms (See Table 62 in the Clinical Study Report for the AMBER Trial). However, the various pooling strategies resulted in relatively similar percentages and between-group differences.

**Table 27. Clinical ADRs, All Grades, Reported in at least 2% of participants in either group of the AMBER trial through Week 48**

| Preferred Term | D/C/F/TAF N=362 N (%) | D/C/F/TDF N=363 N (%) |
|---|---|---|
| Diarrhea | 31 (9) | 40 (11) |
| Rash[1] | 29 (8) | 27 (7) |
| Nausea | 20 (6) | 36 (10) |
| Fatigue[2] | 15 (4) | 15 (4) |
| Headache | 12 (3) | 6 (2) |
| Abdominal discomfort[3] | 8 (2) | 13 (4) |
| Flatulence | 7 (2) | 2 (1) |

*Source: FDA Analysis, JReview 11.0, ADAE and ADSL datasets*

[1]Combined reported terms: dermatitis, dermatitis allergic, erythema, photosensitivity reaction, rash, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash pruritic, toxic skin eruption, urticaria

[2]Combined reported terms: fatigue, asthenia

[3]Combined reported terms: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, abdominal pain lower

In the D/C/F/TAF group, all ADRs listed in Table 27 above were Grade 1 or 2.

**Table 28. Clinical ADRs, Grade 2-4, Reported in at least 2% of participants in either group of the AMBER trial through Week 48**

| Preferred Term | D/C/F/TAF N=362 N (%) | D/C/F/TDF N=363 N (%) |
|---|---|---|
| Rash[1] | 15 (4) | 12 (3) |
| Diarrhea | 7 (2) | 8 (2) |
| Nausea | 3 (1) | 10 (3) |

*Source: FDA Analysis, JReview 11.0, ADAE and ADSL datasets*

[1]Combined reported terms: dermatitis allergic, erythema, photosensitivity reaction, rash, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash pruritic

The Applicant's initial proposed table in Section 6.1 of the label (b) (4) [redacted]. Inclusion of ADRs irrespective of severity occurring in at least 2% of participants (Table 27) in the label would convey a broader array of potential ADRs a patient may experience with D/C/F/TAF, which may be meaningful from a quality of life perspective. To provide clarity, the text in Section 6.1 of the label could indicate that most ADRs were Grade 1 or 2, with one Grade 3 ADR (liver injury) and no Grade 4

ADRs. Note: The Applicant agreed to include the proposed Table 27 above but proposed adding an additional column for each group to display Grade 2 or higher events separately. This approach is clear and transparent and acceptable to the Division.

EMERALD Trial

The findings in this trial were similar to the findings in the AMBER trial. No new safety signals were identified.

### 9.4.7. **Laboratory Findings**

AMBER Trial

The Applicant's initial proposed labeling included (b) (4) [redacted]. See Section 9.5.3 for changes in lipid parameters and Section 9.5.4 for changes in serum creatinine and other renal safety parameters. Grade 2 or higher increases in amylase, lipase, creatine kinase, and liver enzymes were minimal with D/C/F/TAF and either similar or more favorable compared to D/C/F/TDF. The Applicant agreed to include a lab table in Section 6 with Grade 2-4 elevations in lipid parameters (triglycerides, total cholesterol and LDL cholesterol), serum creatinine, and serum glucose.

EMERALD Trial

The findings in this trial were similar to the findings in the AMBER trial. No new safety signals were identified.

### 9.4.8. **Vital Signs**

Vital signs including systolic and diastolic blood pressure and heart rate were assessed at screening and specific time points during the study. Clinically relevant findings were to be recorded as an AE. Overall, no safety concerns related to vital signs were identified in either trial. Refer to each individual Clinical Study Report for detailed results (AMBER: Tables 75 and 76; EMERALD: Tables 86 and 87).

#### 9.4.9. **Electrocardiograms (ECGs)**

An ECG was performed at screening to determine eligibility for study participation but not routinely during study because ECG changes were not expected based on prior studies, including QT studies.

#### 9.4.10. **QT**

Thorough QT studies were not performed with D/C/F/TAF FDC and deemed not necessary for this NDA. The safety of D/C/F/TAF on the QT interval is based on studies performed with the individual components, none of which revealed any cardiac safety concerns.

#### 9.4.11. **Immunogenicity**

Because the individual components of D/C/F/TAF are small molecules and not peptides, immunogenicity was not anticipated and therefore not specifically evaluated in clinical trials.

### 9.5. **Analysis of Submission-Specific Safety Issues**

The following safety issues were selected for further discussion based on known effects of one or more of the individual components of D/C/F/TAF; known class effects; identification as being of potential importance based on earlier clinical data; and/or identification from high-level safety analysis discussed in previous sections of this review. These safety events are also included or proposed for inclusion in the D/C/F/TAF label. Additional safety issues, including adverse events of interest identified by the Applicant, were reviewed but are not discussed in this section because the findings were not clinically important for labeling.

- Skin and Subcutaneous Events
- Hepatic Events
- Lipid Events
- Renal Events
- Bone Events

### 9.5.1. Skin and Subcutaneous Events

AMBER Trial

This analysis was conducted to assess the proposed labeling of the Warning and Precaution Severe Skin Reactions; the Sponsor's initial proposal is based on the DRV/r development program and lacks clinical trial results from D/C/F/TAF trials. Skin and subcutaneous reactions irrespective of causality from the AMBER trial is summarized in Table 29. See 9.4.3 and 9.4.4 for additional details.

**Table 29. Skin and Subcutaneous Reactions, with Associated Results from Laboratory Investigations, through Week 48, AMBER trial**

| | **D/C/F/TAF N=362** N (%) | **D/C/F/TDF N=363** N (%) |
|---|---|---|
| **Skin and subcutaneous reaction**[1] | 53 (15) | 48 (13) |
| Rash[2] | 44 (12) | 37 (10) |
| Stevens-Johnson syndrome | 0 | 1 (<1) |
| Toxic skin eruption | 1 (<1) | 2 (1) |
| Other | 8 (2) | 8 (2) |
| **Maximum grade skin and subcutaneous reaction**[1] | | |
| Grade 1 | 35 (10) | 26 (7) |
| Grade 2 | 18 (5) | 19 (5) |
| Grade 3 | 0 | 1 (<1) |
| Grade 4 | 0 | 2 (1) |
| **Serious skin and subcutaneous reaction**[1] | 0 | 5 (1) |
| Deaths | 0 | 0 |
| **Skin and subcutaneous reaction**[1] **resulting in discontinuation** | 6 (2) | 10 (3) |
| **Time to event**[1] **[days],** Median (Q1, Q3) | 11 (9, 34) | 13 (9, 70) |

*Source: FDA Analysis, JReview 11.0, ADAE, ADLB, and ADSL datasets*
[1]Combined reported terms: dermatitis, dermatitis allergic, erythema, photosensitivity reaction, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, Stevens-Johnson syndrome, toxic skin eruption, urticaria
[2]Combined reported terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic

Overall, skin and subcutaneous events were numerically higher with D/C/F/TAF, but serious and severe (Grade 3 or higher) events were only reported with D/C/F/TDF. Despite these imbalances, the numbers are too few to establish whether the rate or severity of skin and subcutaneous reactions truly differs with D/C/F/TAF compared to D/C/F/TDF.

The Applicant appropriately retains the inclusion of a Warning and Precaution for Severe Skin Reactions in the D/C/F/TAF proposed label. However, the proposed warning states that (b) (4) Even though SJS occurred only in the comparator group, the warning should convey that SJS was also reported with DRV/c (Applicant accepted).

In both the Prezista and Prezcobix labels, rash events occurring in clinical trials with these products are briefly summarized in the Warning and Precaution. A similar presentation for D/C/F/TAF based on the AMBER trial should be included in the SYMTUZA Warning and Precaution. The Applicant accepted the following language: Rash events of any cause and any grade occurred in 15% of subjects with no prior antiretroviral treatment history treated with SYMTUZA in the AMBER trial. Rash events were mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in subjects using D/C/F/TAF was 2%.

EMERALD Trial

Similar PTs indicating a skin reaction as reported in the AMBER trial were also reported in the EMERALD trial. The rate of reactions was higher with D/C/F/TAF (7%, 53/763) compared to the control arm (3%, 13/378), which may be explained by the D/C/F/TAF being the only group receiving new treatment, while the control arm remained on a stable regimen. None of the reactions were serious or severe (Grade 3 or higher), and most (45/53 with D/C/F/TAF) were Grade 1. One event (pruritus) led to discontinuation of D/C/F/TAF. Occurrence of skin reactions in participants who switched from DRV/c or DRV/r with FTC/TDF to D/C/F/TAF suggest TAF and/or COBI may also contribute to these reactions. Overall, labeling is adequate.

### 9.5.2. **Hepatic Safety**

AMBER Trial

A total of 2 (1%) and 5 (1%) participants in the D/C/F/TAF and D/C/F/TDF groups, respectively, reported AEs in the Hepatobiliary SOC. A review of the PTs including causality and severity, did not raise new or additional safety concerns.

Treatment-emergent maximum toxicity grades for ALT, AST, alkaline phosphatase (ALP), total bilirubin, and direct bilirubin were evaluated (Table 30) along with hepatic AEs. The hepatic safety profile exhibited in the AMBER trial was compared to the proposed Hepatotoxicity Warning and Precaution in the label, which stems from the Prezista label. The initial proposed label, of note, (b) (4).

**Table 30. Hepatic Laboratory Abnormalities in the AMBER trial through Week 48**

| Parameter | Analysis Toxicity Grade | D/C/F/TAF N=358 N (%) | D/C/F/TDF N=358 N (%) |
|---|---|---|---|
| ALT | Grade 1: 1.25 to <2.5 x ULN | 14 (4) | 17 (5) |
| | Grade 2: 2.5 to <5.0 x ULN | 1 (<1) | 6 (2) |
| | Grade 3: 5.0 to <10.0 x ULN | 4 (1) | 2 (1) |
| | Grade 4: ≥10.0 x ULN | 1 (<1) | 1 (<1) |
| AST | Grade 1: 1.25 to <2.5 x ULN | 27 (8) | 26 (7) |
| | Grade 2: 2.5 to <5.0 x ULN | 3 (1) | 4 (1) |
| | Grade 3: 5.0 to <10.0 x ULN | 4 (1) | 4 (1) |
| | Grade 4: ≥10.0 x ULN | 0 (0) | 2 (1) |
| ALP | Grade 1: 1.25 to <2.5 x ULN | 2 (1) | 7 (2) |
| | Grade 2: 2.5 to <5.0 x ULN | 0 (0) | 3 (1) |
| Direct bilirubin | Grade 3: >ULN, other signs/symptoms of hepatoxicity | 2 (1) | 0 (0) |
| Total bilirubin | Grade 1: 1.1 to <1.6 x ULN | 10 (3) | 5 (1) |

*Source: FDA Analysis, JReview 11.0, ADLB and ADSL datasets*

Overall, laboratory abnormalities Grade 2-4 were infrequent and similar between groups. None of the participants in either group met Hy's law laboratory criteria. One hepatobiliary SAE/death with D/C/F/TDF was reported (see Section 9.4.2).

Six participants in each group had a Grade 3 or 4 elevation in ALT and/or AST and/or direct bilirubin. In all cases except one, either a plausible alternate etiology (e.g., acute hepatitis C, hepatitis A, alcohol poisoning) was reported or no AEs were reported at the time of the event. In the D/C/F/TAF group, one PT of interest, liver injury, was reported at Day 14 (USUBJID (b) (6) ) and assessed as possibly related to study drug. Maximum laboratory values were ALT 426 U/L, AST 215 U/L, and direct bilirubin 0.5 mg/dL. The participant was asymptomatic, and the event resolved after 10 days with continued dosing. None of these events raised any new safety concerns.

Overall, these findings do not warrant changes to the Hepatotoxicity Warning and Precaution in the proposed label. Any proposed changes to the Hepatotoxicity Warning and Precaution are based on a cross labeling review with the Prezista and Prezcobix labels. Exclusion of hepatic laboratory results from the table of laboratory abnormalities in Section 6.1 is reasonable due to relatively low rates of Grade 2-4 elevations. However, a brief statement summarizing hepatic laboratory abnormalities in Section 6.1 is recommended because of the Hepatotoxicity Warning and Precaution. The Applicant agreed to include the following statement in Section 6 of the label: ALT and/or AST elevations (Grade 2-4 combined) occurred in 2% of adult subjects receiving SYMTUZA with no antiretroviral treatment history in AMBER (Week 48 Analysis). Results were consistent in subjects receiving PREZCOBIX+FTC/TDF.

EMERALD Trial

No new hepatic safety issues were identified in the switch trial. Hepatic lab abnormalities occurred at a similar or lower rate with D/C/F/TAF compared to the control group. Grade 2-4 ALT and/or AST elevations occurred in 3% of participants in the D/C/F/TAF group compared to 3-4% in the bPI/F/TDF group. Total bilirubin elevations occurred in <1% of participants in the D/C/F/TAF group compared to 14% in the bPI/F/TDF group; this difference was driven by participants receiving an ATV-based regimen which is known to cause hyperbilirubinemia. PTs in the SOC Hepatobiliary Disorders were reported in 1% of participants in each group, none of which were related to study treatment.

### 9.5.3. **Changes in Lipid Parameters**

AMBER Trial

Separate clinical trials with DRV (boosted with RTV) and TAF (with E/C/F/TAF) have shown increases in lipid parameters, but trials are generally too small to determine the clinical significance of these changes. Lipid analysis conducted for D/C/F/TAF mirrors the analyses conducted for most other ARV clinical trials.

The following lipid table (Table 31) was agreed upon by FDA and the Applicant for inclusion in the label. The table is slightly revised from the Applicant's original proposal by: (b) (4) The results were confirmed in JReview. All lipid parameters increased to a greater degree with D/C/F/TAF compared to D/C/F/TDF, which is consistent with findings from prior TAF versus TDF trials.

**Table 31. Lipid Values, Mean Change from Baseline to Week 48 in the AMBER Trial[a]**

(b) (4)

*Source: Applicant's Analysis, Response to FDA Request submitted to the NDA on 09Feb2018*

(b) (4)

The portions highlighted in gray will be included in the label, (b) (4)

(b) (4)

*Source: FDA Analysis, JReview 11.0, ADLB and ADSL datasets*

EMERALD Trial

All lipid parameters increased to a greater degree when switching to D/C/F/TAF compared to continuing the baseline PI (bPI)/F/TDF (Table 33 and Table 35), which is consistent with findings from prior TAF versus TDF trials. Though the clinical significance of these findings is unknown on a population level, the degree of increase for certain parameters (e.g., LDL) may be concerning for an individual patient depending on baseline lipid values and other risk factors. Because these findings are generally similar to the AMBER results, additional labeling is not warranted.

**Table 33. Lipid Values, Mean Change from Baseline to Week 48 in the EMERALD Trial**

| | SYMTUZA N=633 | | bPI+F/TDF N=315 | |
|---|---|---|---|---|
| | Baseline | Week 48 | Baseline | Week 48 |
| Mean[b] | mg/dL | Change | mg/dL | Change |
| | n=570[c] | | n=277[d] | |
| Total cholesterol | 187 | +22 | 185 | +1 |
| HDL cholesterol | 50 | +3 | 50 | -1 |
| LDL cholesterol | 110 | +18 | 108 | +1 |
| Triglycerides | 138 | +9 | 139 | +8 |
| Total cholesterol to HDL ratio | 4.0 | 0.2 | 4.0 | 0.1 |

bPI = boosted protease inhibitor; F/TDF = emtricitabine/tenofovir disoproxil fumarate; HDL = high-density lipoprotein; HIV-1 = human immunodeficiency virus type 1; LDL = low-density lipoprotein; N = number of subjects in intent-to-treat population[a]; n = number of subjects with data at Week 48; TC = total cholesterol; TC/HDL = total cholesterol to HDL cholesterol ratio.

[a] Subjects on lipid-lowering agents at screening/baseline were excluded from the analysis (130 out of 763 subjects on SYMTUZA, 63 out of 378 subjects on bPI+F/TDF). Subjects initiating a lipid-lowering agent post-baseline had their last fasted on-treatment value (prior to starting the agent) carried forward (20 on SYMTUZA, 7 on bPI+F/TDF).

[b] The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week-48 values, or the last value carried forward prior to initiating lipid-lowering agent post-baseline.

[c] n=570 for total cholesterol (TC), 568 for triglycerides, 567 for HDL and TC/HDL, 565 for LDL.

[d] n=277 for TC and triglycerides, n=276 for HDL, LDL and TC/HDL.

Source: ad hoc analysis

*Source: Applicant's Analysis, Response to FDA Request submitted to the NDA on 09Feb2018*

**Table 34. Lipid Abnormalities, Treatment-Emergent Maximum Toxicity Grade, in the EMERALD trial through Week 48**

| Toxicity Name | Analysis Toxicity Grade | D/C/F/TAF | Control |
|---|---|---|---|
| Cholesterol, fasting | Grade 1: 200 to <240 mg/dL | 172 (23%) | 67 (18%) |
| | Grade 2: 240 to <300 mg/dL | 160 (21%) | 27 (7%) |
| | Grade 3: ≥ 300 mg/dL | 28 (4%) | 5 (1%) |
| LDL, fasting | Grade 1: 130 to <160 mg/dL | 154 (20%) | 50 (13%) |
| | Grade 2: 160 to <190 mg/dL | 119 (16%) | 17 (5%) |
| | Grade 3: ≥ 190 mg/dL | 48 (6%) | 6 (2%) |
| Triglycerides, fasting | Grade 1: 150 to 300 mg/dL | 140 (18%) | 62 (17%) |
| | Grade 2: >300 to 500 mg/dL | 41 (5%) | 23 (6%) |
| | Grade 3: >500 to <1,000 mg/dL | 11 (1%) | 8 (2%) |
| | Grade 4: >1,000 mg/dL | 3 (<1%) | 0 (0%) |

*Source: FDA Analysis, JReview 11.0, ADLB and ADSL datasets*

### 9.5.4. **Renal Safety**

The renal safety profile with TAF versus TDF in combination with COBI was previously evaluated in the elvitegravir(E)/C/F/TAF (Genvoya) development program. The association between TDF and renal toxicity is well known and can include Fanconi syndrome or acute renal failure in its more severe form. Renal toxicity is related to higher systemic exposures of the active form, tenofovir diphosphate (TFV), which accumulates in the renal proximal tubules. Because TAF compared to TDF results in lower systemic exposures of TFV, TAF has been associated with a more favorable renal safety profile. Separately, COBI is known to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting glomerular filtration.

This review compares the renal safety profile of TAF and TDF when coadministered with DRV/c (and FTC), as assessed by renal AEs and laboratory results. Of note, the Applicant included a Warning and Precaution for New Onset or Worsening Renal Impairment based on cross-labeling with COBI- and TAF-containing labels. However, the Applicant's initial proposal did not include (b) (4) .

Based on the analyses below (Table 35, Table 36, and Table 39) and the Genvoya, Stribild, and Tybost labels, we proposed inclusion of Renal Laboratory Tests in Section 6.1 of the label for both the AMBER and EMERALD trials (Applicant agreed). The Applicant also included median baseline value and mean change from baseline to Week 48 for UPCR, which is acceptable. Similar UPCR information was included in the initial Genvoya labels with Week 48 and Week 96 data, based on consult recommendations from FDA's Division of Cardiovasular and Renal Products (DCRP).

<u>AMBER Trial</u>

A total of 7 (2%) and 21 (7%) participants in the D/C/F/TAF and D/C/F/TDF groups, respectively, reported AEs in the Renal and Urinary Disorders SOC. All events were Grade 1 or 2. One event (proteinuria) in the D/C/F/TAF group was deemed related to study drug, compared to six events in the D/C/F/TDF group (glycosuria, proteinuria, renal failure, renal impairment, and micturition urgency).

Increases in serum creatinine occurred in both treatment groups and were mostly Grade 1-2. The rate of Grade 2 elevations was higher in the D/C/F/TDF group (Table 35). A single Grade 4 elevation occurred in the D/C/F/TAF group. This participant experienced transient serum creatinine elevation from normal values to 3.5 mg/dL with resolution within two days with continued treatment and no associated clinical AEs.

**Table 35. Serum Creatinine and eGFR by Maximum Toxicity Grade in the AMBER trial through Week 48**

| Parameter | Analysis Toxicity Grade | D/C/F/TAF N=358 N (%) | D/C/F/TDF N=358 N (%) |
|---|---|---|---|
| Serum Creatinine | Grade 1: 1.1 to 1.3 x ULN | 4 (1) | 5 (1) |
| | Grade 2: 1.3 to 1.8 x ULN OR Increase to 1.3 to <1.5 x BL | 15 (4) | 49 (14) |
| | Grade 4: ≥3.5 x ULN OR Increase of ≥2.0 x BL | 1 (<1) | 0 |
| $eGFR_{CG}$ | Grade 2: <90 to 60 mL/min OR 10 to <30% decrease from BL | 69 (19) | 94 (27) |
| | Grade 3: <60 to 30 mL/min OR 30 to <50% decrease from BL | 4 (1) | 9 (3) |
| $eGFR_{CKD-EPI}$ | Grade 2: <90 to 60 mL/min/1.73m$^2$ OR 10 to <30% decrease from BL | 129 (36) | 135 (38) |
| | Grade 3: <60 to 30 mL/min/1.73m$^2$ OR 30 to <50% decrease from BL | 5 (1) | 9 (3) |
| | Grade 4: <30 mL/min/1.73m$^2$ OR >50% decrease from BL or dialysis | 1 (<1) | 0 |

*Source: FDA Analysis, JReview 11.0, ADLB and ADSL datasets*
$eGFR_{CG}$ = estimated glomerular filtration rate calculated by the Cockcroft-Gault formula
$eGFR_{CKD-EPI}$ = estimated glomerular filtration based on serum creatinine calculated by the CKD-EPI formula

Table 36 shows the median (Q1, Q3) serum creatinine and estimated glomerular filtration rate (eGFR) based on the Cockcroft-Gault formula at baseline, Week 2, and Week 48, and changes from baseline at Week 2 and Week 48. Estimated GFR results using the CKD-EPI formula (not shown) were not clinically different. Additionally, the mean changes from baseline in both groups (not shown) were similar to the median changes. Changes occurred by Week 2 and remained consistent through Week 48. The changes were relatively low in both groups but numerically greater in the D/C/F/TDF group. Overall, the degree of reduction in eGFR through Week 48 with D/C/F/TAF is unlikely to be clinically significant for most patients with baseline eGFR values in the normal range.

**Table 36. Serum Creatinine and eGFR Median Change from Baseline in the AMBER trial through Week 48**

| | D/C/F/TAF | | | D/C/F/TDF | | |
|---|---|---|---|---|---|---|
| **Serum Creatinine** | | | | | | |
| | N | Median (Q1, Q3) | | N | Median (Q1, Q3) | |
| | | Analysis Value (mL/min) | Δ from Baseline | | Analysis Value (mL/min) | Δ from Baseline |
| Baseline | 362 | 0.90 (0.80, 1.00) | -- | 363 | 0.89 (0.79, 0.98) | -- |
| Week 2 | 347 | 0.94 (0.85, 1.04) | 0.05 (-0.01, 0.10) | 346 | 0.97 (0.87, 1.09) | 0.09 (0.02, 0.15) |
| Week 48 | 340 | 0.95 (0.86, 1.05) | 0.06 (0.00, 0.11) | 330 | 0.97 (0.87, 1.10) | 0.10 (0.01, 0.16) |
| **Estimated Glomerular Filratation Rate (eGFR) – Cockcroft-Gault** | | | | | | |
| | N | Median (Q1, Q3) | | N | Median (Q1, Q3) | |
| | | Analysis Value (mL/min) | Δ from Baseline | | Analysis Value (mL/min) | Δ from Baseline |
| Baseline | 362 | 119 (105, 135) | -- | 363 | 118 (103, 138) | -- |
| Week 2 | 347 | 111 (97, 133) | -6 (-14, 1) | 346 | 109 (93, 127) | -10 (-18, -2) |
| Week 48 | 340 | 113 (97, 131) | -5 (-14, 4) | 330 | 109 (93, 126) | -12 (-20, -3) |

*Source: FDA Analysis, JReview 11.0, ADLB and ADSL datasets*

Table 37 and Table 38 show quantitative proteinuria and albuminuria results based on urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR). Most participants had no clinically significant proteinuria or albuminuria at baseline, and relatively few worsened at Week 48. Median UPCR values in the D/C/F/TAF and D/C/F/TDF groups, respectively, were 47 mg/g and 51 mg/g at baseline and 30 mg/g and 35 mg/g at Week 48. The rate of new onset UPCR or UACR trended higher with D/C/F/TDF compared to D/C/F/TAF.

**Table 37. Quantitative Proteinuria and Albuminuria Results in Participants with Normal Baseline UPCR and UACR in the AMBER Trial through Week 48**

| | D/C/F/TAF | D/C/F/TDF |
|---|---|---|
| Baseline UPCR ≤200 mg/g | n=323 | n=308 |
| UPCR ≥200 mg/g | 2 (1%) | 11 (4%) |
| Baseline UACR ≤30 mg/g | n=322 | n=310 |
| UACR 30 to 300 mg/g | 8 (3%) | 11 (4%) |
| UACR ≥300 mg/g | 0 | 0 |

*Source: FDA Analysis, JReview 11.0, ADLB and ADSL datasets*

Of the participants with proteinuria or albuminuria at baseline, most improved at Week 48, suggesting a possible improvement in HIV nephropathy with ART initiation. Notably, the rate of improvement in UPCR and UACR in this subpopulation was similar across both groups; this finding does not support the Applicant's proposed statement (b) (4) (Applicant agreed to remove).

**Table 38. Quantitative Proteinuria and Albuminuria Results in Participants with Elevated Baseline UPCR and UACR in the AMBER Trial through Week 48**

| | D/C/F/TAF | D/C/F/TDF |
|---|---|---|
| Baseline UPCR ≥200 mg/g | n=13 | n=17 |
| UPCR ≤200 mg/g | 11 (85%) | 14 (82%) |
| Baseline UACR 30-300 mg/g | n=15 | n=14 |
| UACR ≤30 mg/g | 11 (73%) | 10 (71%) |
| Baseline UACR ≥300 mg/g | n=1 | n=3 |
| UACR ≤30 | 0 | 2 |
| UACR 30 to 300 mg/g | 1 | 0 |

*Source: FDA Analysis, JReview 11.0, ADLB and ADSL datasets*

In the AMBER trial, subclinical proximal renal tubulopathy (PRT) was defined as a serum creatinine increase ≥0.40 mg/dL plus one of the following confirmed changes from baseline: (1) ≥2 grade level increase in graded proteinuria; (2) ≥1 grade level increase in graded hypophosphatemia; or (3) ≥1 grade level increase in graded glycosuria. A summary of the Applicant's analysis of subclinical PRT is available in Table 32 of the Clinical Study Report for the AMBER trial. This table was confirmed by FDA analysis using JReview. Overall, no participants in the D/C/F/TAF group experienced subclinical PRT compared to two participants in the D/C/F/TDF group.

EMERALD Trial

The renal safety profile when switching from TAF versus TDF in combination with COBI was previously evaluated in the elvitegravir(E)/C/F/TAF (Genvoya) development program. The D/C/F/TAF program evaluated a switch when the regimen included a boosted PI. In both groups, the mean changes in serum creatinine and eGFR from baseline at Week 48 was negligible as displayed in Table 39.

**Table 39. Serum Creatinine and eGFR Median Change from Baseline in the EMERALD trial through Week 48**

| | D/C/F/TAF | | | bPI/F/TDF | | |
|---|---|---|---|---|---|---|
| **Serum Creatinine** | | | | | | |
| | N | Median (Q1, Q3) | | N | Median (Q1, Q3) | |
| | | Analysis Value (mL/min) | Δ from Baseline | | Analysis Value (mL/min) | Δ from Baseline |
| Baseline | 761 | 0.97 (0.86, 1.10) | -- | 378 | 0.98 (0.86, 1.10) | -- |
| Week 2 | 740 | 1.00 (0.87, 1.10) | 0.00 (-0.05, 0.10) | 355 | 0.99 (0.86, 1.10) | 0.00 (-0.03, 0.10) |
| Week 48 | 727 | 1.00 (0.88, 1.10) | 0.00 (-0.06, 0.10) | 350 | 0.97 (0.84, 1.10) | 0.00 (-0.08, 0.10) |
| **Estimated Creatinine Clearance – Cockcroft-Gault** | | | | | | |
| | N | Median (Q1, Q3) | | N | Median (Q1, Q3) | |
| | | Analysis Value (mL/min) | Δ from Baseline | | Analysis Value (mL/min) | Δ from Baseline |
| Baseline | 761 | 104 (87, 122) | -- | 378 | 103 (86, 122) | -- |
| Week 2 | 740 | 102 (85, 120) | -1 (-9, 5) | 355 | 103 (85, 123) | -1 (-7, 5) |
| Week 48 | 727 | 103 (86, 122) | -1 (-9, 8) | 350 | 105 (84, 125) | -1 (-8, 8) |

*Source: FDA Analysis, JReview 11.0, ADLB and ADSL datasets*

However, quantitative proteinuria results were more favorable with D/C/F/TAF versus the control group: 83% (45/54) compared to 44% (17/39) of participants with baseline UPCR ≥200 mg/g, respectively, demonstrated an improvement in UPCR to <200 mg/g at Week 48. Between-group differences in the rate of improvement of UACR was similar. Few participants (2%) in the D/C/F/TAF group with baseline UPCR <200 mg/g and/or baseline UACR <30 mg/g experienced a worsening at Week 48. Median UPCR values in the D/C/F/TAF and control groups, respectively, were 62 mg/g and 63 mg/g at baseline and 37 mg/g and 53 mg/g at Week 48.

These analyses suggest that switching to D/C/F/TAF compared to continuing bPI/F/TDF may reduce quantitative proteinuria, but improvement in serum creatinine and eGFR appears minimal.

#### 9.5.5. **Bone Safety**

Bone substudies within the AMBER and EMERALD trials evaluated BMD by dual-energy X-ray absorptiometry (DXA) at baseline, Week 24, and Week 48, as well as bone biomarkers. The Applicant's initial proposed labeling included (b) (4) Please see Dr. Stephen Voss's review for complete analysis and recommendations.

Dr. Voss confirmed the Sponsor's results for both substudies and concluded that D/C/F/TAF is associated with significantly more favorable BMD changes than D/C/F/TDF or bPI/F/TDF. Dr. Voss also noted the changes are consistent with observed changes in markers of bone turnover and with findings from prior TAF versus TDF treatment-naïve and switch trials. With respect to labeling of results in individual responders, Dr. Voss recommends reporting only the proportion of patients with ≥5% BMD decline at the lumbar spine and ≥7% decline at the femoral neck based on estimated degrees of bone loss that are potentially clinically significant with respect to fracture risk and accounting for the degree of precision of the DXA measurements. Labeling of AEs related to fractures or biomarker data is not necessary. The Applicant accepted all recommendations.

### 9.6. **Safety Analyses by Demographic Subgroups**

<u>Sex</u>

In the AMBER trial, most participants (88%) in both groups were male (Table 6). A similar percentage of males (48%) and females (50%) in the D/C/F/TAF group experienced at least one AE listed in Table 27, but a higher percentage of females (43%) versus males (23%) experienced one of these AEs that was assessed as related to D/C/F/TAF. Table 40 lists AEs irrespective of causality that occurred at a difference of at least 5% between sexes in the D/C/F/TAF group. Diarrhea occurred more commonly in males, while rash and nausea occurred more commonly in females receiving D/C/F/TAF. In the D/C/F/TDF group (not shown), similar differences were observed for rash and nausea, but diarrhea occurred at a similar rate in both sexes. Differences between sexes for individual AEs were relatively unchanged when considering only drug-related AEs. Interpretation of clinical significance of these differences in the AMBER trial is difficult due to the relatively small sample size of females.

**Table 40. Selected Clinical AEs, All Grades, Irrespective of Causality, By Sex in the D/C/F/TAF Group of the AMBER trial through Week 48**

| Preferred Term | Male N=318 N (%) | Female N=44 N (%) |
|---|---|---|
| Diarrhea | 66 (21) | 5 (11) |
| Rash[1] | 44 (14) | 9 (20) |
| Nausea | 19 (6) | 9 (20) |

*Source: FDA Analysis, JReview 11.0, ADAE and ADSL datasets*

[1]Combined reported terms: dermatitis, dermatitis allergic, erythema, photosensitivity reaction, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, toxic skin eruption, urticaria

In the EMERALD trial, most participants (82%) were male, but the female sample size was larger (n=141 in the D/C/F/TAF group) than the AMBER trial. Diarrhea occurred more frequently in males (9%) versus females (3%), while headache occurred more frequently in females (13%) versus males (6%) who received D/C/F/TAF. Rash and nausea with D/C/F/TAF occurred at a similar rate between sexes in this trial. Overall, none of these differences warrant labeling.

Race

In the AMBER trial, most participants (83%) in both groups were White, distantly followed by Black/African American (AA) (11%) (Table 6). Because too few participants were Asian, American Indian/Native Alaskan, or Other (Table 6), these groups were excluded from safety analysis by race. A similar percentage of White versus Black/AA participants in the D/C/F/TAF group experienced at least one AE listed in Table 27 (all cause 48%; related 25-28%). Table 41 lists AEs irrespective of causality that occurred at a difference of at least 5% between White and Black/AA participants in the D/C/F/TAF group. Diarrhea occurred more commonly in White participants, while nausea and abdominal pain occurred more commonly in Black/AA participants receiving D/C/F/TAF. Interpretation of clinical significance of these differences in the AMBER trial is difficult due to the relatively small sample size of Black/AA participants. In the D/C/F/TDF group (not shown), the rate of each AE in Table 27 irrespective of causality was similar in White versus Black/AA participants.

Because too few participants in each group were Asian (1-2%), American Indian/Native Alaskan (< 1%), or Other (3-4%), interpretation of safety analysis by race in these groups is difficult. Therefore, these races are not included in Table 41.

**Table 41. Selected Clinical AEs, All Grades, Irrespective of Causality, By Race in the D/C/F/TAF Group of the AMBER trial through Week 48**

| Preferred Term | White N=300 N (%) | Black/African American N=40 N (%) |
|---|---|---|
| Diarrhea | 61 (20) | 5 (13) |
| Nausea | 20 (7) | 6 (15) |
| Abdominal pain[1] | 14 (5) | 5 (13) |

*Source: FDA Analysis, JReview 11.0, ADAE and ADSL datasets*
[1]Combined reported terms: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, abdominal pain lower

Like the AMBER trial, the EMERALD trial participants were overall mostly White (76%), distantly followed by Black/African American (AA) (21%), with few Asian (2%), American Indian/Native Alaskan (< 1%), or Other (< 1%) (Table 12). In this trial, no differences in safety were observed for White versus Black/AA participants in either treatment group. Though the number of Asian participants was too few to conduct a meaningful safety analysis, the most common AEs did not appear disproportionately higher in this racial group.

Age

In the AMBER trial, only one participant across both groups was aged 65 years and older. Therefore, it was not feasible to conduct safety analysis by age, particularly for older adults in whom the safety profile may differ.

In the EMERALD trial, 25 participants in the D/C/F/TAF group were aged 65 years and older. Though the number of older participants was also too few to conduct a meaningful safety analysis, the most common AEs did not appear disproportionately higher in the 65 year and older age group.

## 9.7. Safety in the Postmarket Setting

### 9.7.1. Safety Concerns Identified Through Postmarket Experience

Current labeling for approved products containing components of D/C/F/TAF were the source of identifying postmarketing safety concerns. Only the Prezista (DRV) label contained postmarket safety information relevant to D/C/F/TAF, and as such, the terms in Section 6.2 from the Prezista label will be included in the D/C/F/TAF label. Section 6.2 in the Tybost (COBI) and Descovy (F/TAF) labels do not currently specify any safety concerns identified through postmarket experience. No safety concerns were identified for DRV/c in the FDAAA Section 915 Postmarket Safety Summary Analysis completed on August 4, 2017.

### 9.7.2. Expectations on Safety in the Postmarket Setting

Safety of D/C/F/TAF in the postmarket setting is not expected to differ from the safety profile observed with the individual components.

## 10 Advisory Committee Meeting and Other External Consultations

None

## 11 Pediatrics

**Adolescents and Pediatric Deferral**

Efficacy studies of D/C/F/TAF were conducted in adults. Based on prior studies in adolescents with the components of D/C/F/TAF, the applicant proposed that D/C/F/TAF be approved in adolescents (b) (4). The Agreed Initial Pediatric Study Plan (iPSP) states that approval of D/C/F/TAF in adolescents will depend on: (1) approval of D/C/F/TAF in adults; (2) bioequivalence of D/C/F/TAF to the single agents; and (3) established doses of DRV, COBI, FTC, and TAF in adolescents from various adolescent PK studies matching the exposure to adults and with supportive safety data in adolescents. The applicant noted that adult doses of DRV, FTC, and TAF are approved in adolescents and cited the following pediatric PK data to support adolescent approval (NDA 210455 SDN 15 and SDN 20):

- In a study of adults and adolescents administered the adult dose of DRV/c, DRV and COBI exposures were similar in adults and adolescents.

- In a study of adults and adolescents administered the adult dose of E/C/F/TAF, exposures of all components were similar in adults and adolescents.

- In a study of adults and adolescents administered the adult dose of F/TAF with LPV/r, TAF exposures were similar in adults and adolescents.

We agree the above studies may support approval of D/C/F/TAF in adolescents. However, the adolescent studies of DRV/c and of F/TAF with LPV/r have not been submitted to FDA and some of the data provided are in poster/abstract format. DAVP communicated to the applicant that a PMR for a clinical trial with D/C/F/TAF in adolescents may not be needed if dosing can be supported by prior studies of the components of D/C/F/TAF (see Postmarketing Requirements and Commitments). In other words, submission of the data and FDA review are needed prior to approval in adolescents.

Because adult studies are completed and D/C/F/TAF is ready for approval, FDA is granting a deferral for the adolescent population (≥ 40 kg). The deferral is written for children 3 to <18 years of age weighing ≥40 kg, with the focus on weight rather than age because weight-based dosing is expected.

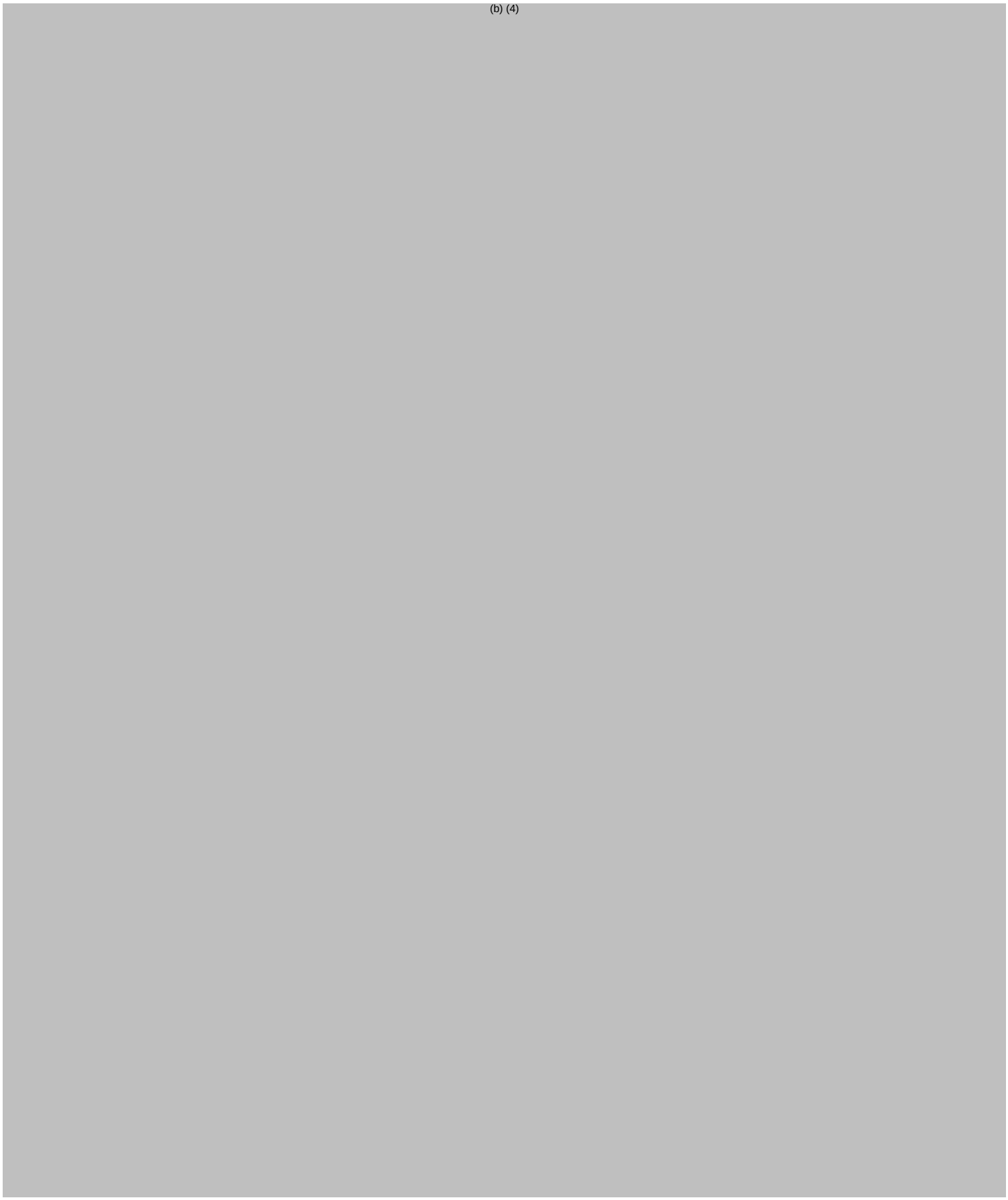
**Pediatric Waivers**

The Applicant is requesting a waiver in children 3 to <18 years of age weighing ≤40 kg because the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients in this group.

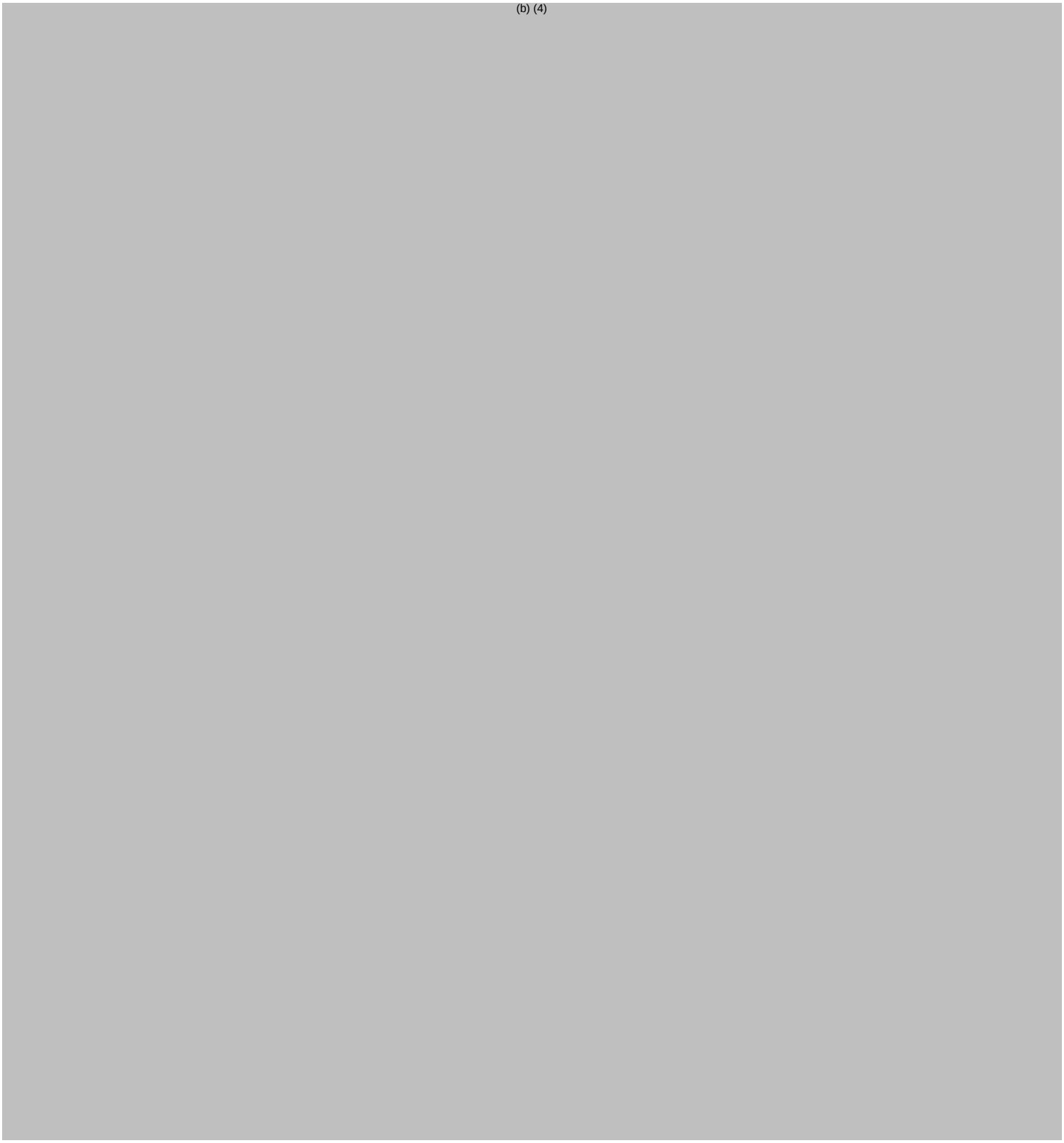
The Applicant is requesting a waiver in children <3 years of age because the product (the DRV component of D/C/F/TAF) would be unsafe in this population. A waiver was previously granted for clinical testing and treatment for DRV in HIV-infected pediatric patients <3 years of age based on toxicity and mortality observed in juvenile rats dosed with DRV.
The Division and the Pediatric Review Committee (PeRC) agree with the Applicant's proposal and rationale for waivers in both respective pediatric groups. Thus, FDA is granting a waiver for ages 3 to <18 years weighing ≤40 kg and for ages <3 years.

## 12 Labeling Recommendations

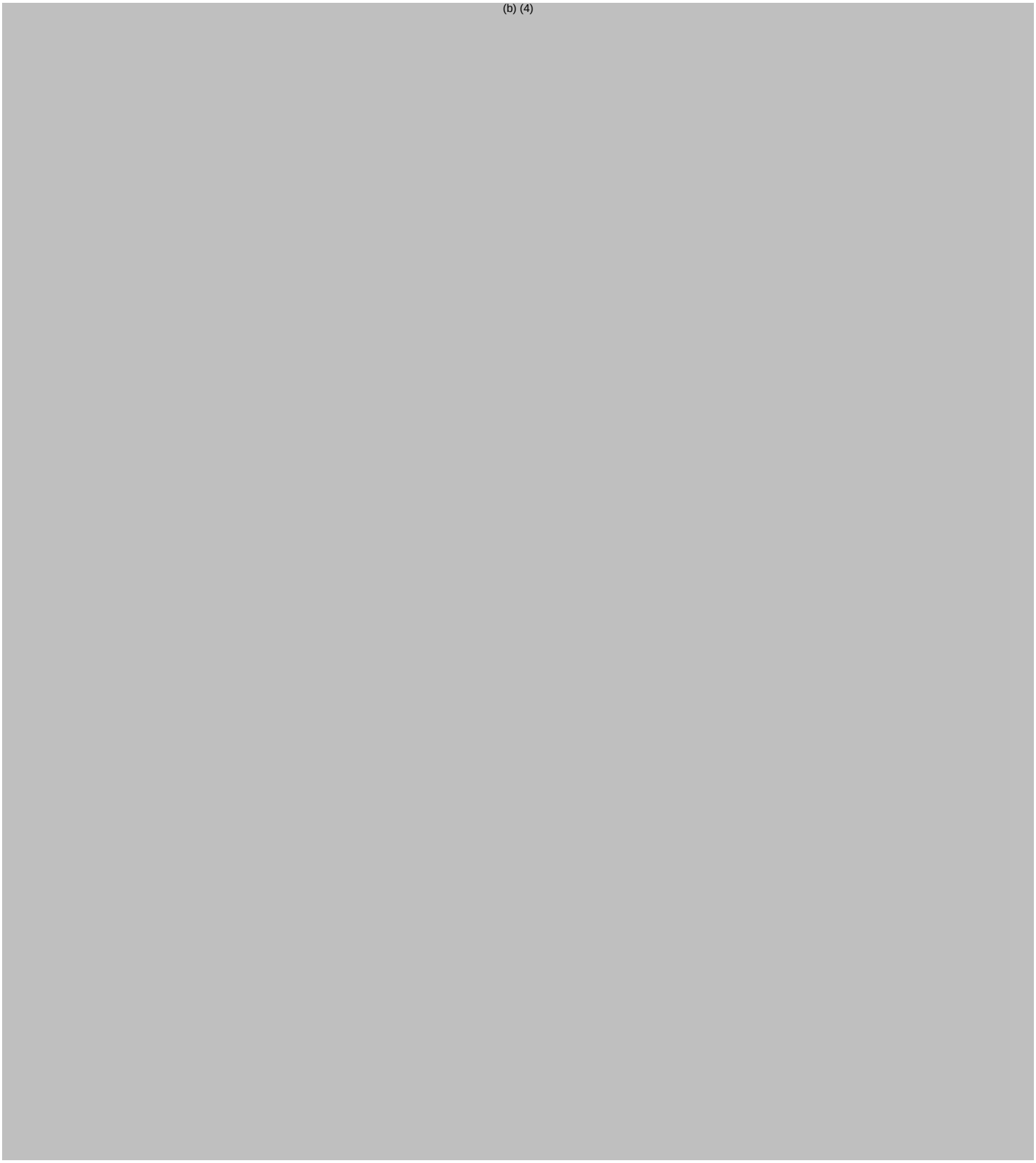
(b) (4)


(b) (4)

(b) (4)



(b) (4)



### 12.2. Patient Labeling

Revisions were made for consistency with the product labeling.

## 13 Risk Evaluation and Mitigation Strategies (REMS)

### 13.1. Safety Issue(s) that Warrant Consideration of a REMS

None

### 13.2. Conditions of Use to Address Safety Issue(s)

Not applicable

### 13.3. Recommendations on REMS

Not applicable

# 14 Postmarketing Requirements and Commitments

The following postmarketing requirement (PMR) is being issued for a pediatric study under the Pediatric Research Equity Act (PREA). The caveat that a clinical trial may not be required is consistent with the agreed iPSP. See Section 11 for details.

- Conduct your deferred pediatric trial in HIV-1 infected patients weighing at least 40 kg to assess the pharmacokinetics, safety, and tolerability, and antiviral activity of darunavir, cobicistat, emtricitabine, and tenofovir alafenamide fixed-dose combination (FDC). Study participants should be monitored for 24 weeks to assess safety and durability of antiviral response. A clinical trial may not be required if the dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual components and if the FDC produces similar exposures as the individual components.

# 15 Appendices

## 15.1. Financial Disclosure

Overall, the financial disclosures do not affect approvability of D/C/F/TAF. One investigator across both trials reported significant financial payments from the sponsor. However, these payments are not expected to effect trial outcomes because:

(1) The investigator enrolled an overall low percentage (3%) of participants in both AMBER and EMERALD.

(2) Janssen's study monitoring verified protocol conformance by all sites.

(3) The primary efficacy endpoint and most submission-specific safety concerns (hepatic, lipid, renal, and bone safety) were assessed by objective measurements.

(4) Both trials were randomized, and AMBER had a double-blind design.

(5) Internal discussions with FDA/OSI regarding recent site inspections (see Section 4.1).

**Covered Clinical Study (Name and/or Number): AMBER**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 125 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 2<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator 0<br>Sponsor of covered study: 0 | | |

| | | |
|---|---|---|
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

Two AMBER investigators reported significant payments of other sorts from the sponsor.

(b) (6) at Site (b) (6) enrolled (b) (6) (screened (b) (6)) of the 725 ((b) (6) %) participants from September 2015 to November 2016. From January 2012 to July 2017, Janssen paid the investigator $58,197 for non-trial activities including (b) (6) . From January 2015 to July 2017, which includes the period the investigator participated in the AMBER and EMERALD (see below) trials, Janssen paid the investigator $12,901 for non-trial activities including (b) (6) .

Christoph Spinner at Site DE10007 enrolled 6 of the 725 (0.8%) participants. Janssen, however, has no record of payment to this investigator for non-trial activities, indicating over reporting by the investigator. Janssen states they contacted the investigator to make the correction.

**Covered Clinical Study (Name and/or Number): EMERALD**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 120 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 1 | | |

| | | |
|---|---|---|
| Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator 0<br>Sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

Significant payments of other sorts from the sponsor were reported for one principal investigator in the EMERALD trial.

(b) (6) at Site (b) (6) enrolled (b) (6) (screened (b) (6)) of the 1141 ((b) (6) %) participants from May 2015 to February 2017. See payment details above for the AMBER trial.

## 15.2. Clinical Pharmacology Individual Study Reviews

### 15.2.1. MC114FD2HTX1001

| | |
|---|---|
| **Study title** | A single-dose, open-label, randomized, crossover study to assess the bioequivalence of darunavir 800 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg, in the presence of cobicistat 150 mg, administered as either a fixed-dose combination tablet or as separate agents in healthy subjects |
| **Study #** | TMC114FD2HTX1001 |
| **Study period** | 11/20/15 – 2/22/16 |

**STUDY SUMMARY (As Reported by the Applicant)**

**OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS**

*Objectives:*
Primary: Relative bioavailability of DRV, FTC, and TAF between D/C/F/TAF vs single agents
Secondary: Relative bioavailability of COBI from D/C/F/TAF vs single agent, safety, tolerability

*Design and study schema:*
Single-dose, open-label, randomized, crossover study.
Treatment A: single oral dose of D/C/F/TAF 800/150/200/10 mg
Treatment B: single oral dose of DRV 800 mg, FTC/TAF 200/10 mg, and COBI 150 mg

| | Session I | at least 7 days washout* | Session II |
|---|---|---|---|
| Group 1 (N=48) | Treatment A | → | Treatment B |
| Group 2 (N=48) | Treatment B | → | Treatment A |

* Day 1 of a treatment session is the first day of the washout period.

*Population:* Healthy adults

*Dose selection:* Approved doses of DRV, COBI, FTC, and TAF were used

*Administration with regard to food:* Fed

*Formulation:*
D/C/F/TAF: G001 (commercial formulation)
DRV, COBI, and FTC/TAF: commercial formulations

*Excluded concomitant medications:* No medications are allowed except paracetamol, ibuprofen, or hormonal contraceptions, or for treatment of rash, nausea, or diarrhea.

*PK sampling:* Intensive sampling (~20 samples) through 72 hours postdose

*Bioanalytical methods:*
(b) (4)

| TAF: 60-1578 |
|---|
| **RESULTS** |
| **Demographics**<br>96 subjects were enrolled and 94 completed the study (two subjects withdrew consent after completing one treatment). Demographics were similar between treatment groups. Mean age was 30 years and mean BMI was 24 kg/m$^2$. Subjects were 54% male, 87% white, and 5% Hispanic. |
| **Protocol Deviations**<br>Five major deviations were reported, all for violations of eligibility criteria (enrolled despite elevated cholesterol). |
| **Concomitant medications**<br>There were no reported uses of prohibited concomitant medications. |
| **Pharmacokinetics**<br>The PK of DRV, COBI, FTC, and TAF were similar between treatment groups, with 90% confidence intervals of Cmax and AUC ratios between 80-125%.<br><br>Ten subjects vomited during the study. PK data from one subject who vomited within twice the median Tmax for that treatment was excluded. Other subjects vomited after twice the median Tmax for the respective treatment and PK data were not excluded. |
| **Safety**<br>There were no deaths, SAEs, or discontinuations due to AEs. |

| **REVIEWER ASSESSMENT** | |
|---|---|
| The study design is acceptable ☑ Yes ☐ No | |
| **Study Conduct** | |
| ▪ Was bioanalytical method performance acceptable? | ☑ Yes ☐ No |
| ▪ Did protocol deviations affect the integrity of the study? | ☐ Yes ☑ No |
| ▪ Did use of prohibited concomitant medications affect the integrity of the study? | ☐ Yes ☑ No |
| **Study Results**<br>Are the study results acceptable as reported by the sponsor? ☑ Yes ☐ No | |
| **Labeling**<br>This study was included in the DRV and TAF popPK models. The popPK modeling underlies labeling statements in section 12.3 regarding the impact of demographic factors on PK. | |
| **References**<br>CSR link<br>\\cdsesub1\evsprod\nda210455\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tmc114fd2htx1001\csr-full-tmc114fd2htx1001.pdf | |

### 15.2.2. TMC114FD2HTX1002

| | |
|---|---|
| **Study title** | A single-dose, open-label, randomized, crossover study to assess the impact of food on the pharmacokinetics of darunavir, cobicistat, emtricitabine, and tenofovir alafenamide administered as a fixed-dose combination tablet, and the relative bioavailability of these antiretrovirals in different formulations/combinations, in healthy subjects |
| **Study #** | TMC114FD2HTX1002 |
| **Study period** | 6/1/15 – 8/14/15 |

| **STUDY SUMMARY (As Reported by the Applicant)** |
|---|
| **OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS** |
| *Objectives:*<br>Primary: Relative bioavailability (relBA) of FTC and TAF as D/C/F/TAF vs E/C/F/TAF, relBA of D/C/F/TAF vs single agents, effect of food on D/C/F/TAF |
| *Design and study schema:*<br>All treatments were a single dose.<br><br><u>Panel 1</u><br>Treatment A: D/C/F/TAF 800/150/200/10 mg<br>Treatment B: E/C/F/TAF 150/150/200/10 mg<br><br><u>Panel 2</u><br>Treatment C: D/C/F/TAF 800/150/200/10 mg<br>Treatment D: DRV 800 mg, FTC/TAF 200/10 mg, COBI 150 mg<br><br><u>Panel 3</u><br>Treatment E: D/C/F/TAF 800/150/200/10 mg<br>Treatment F: D/C/F/TAF 800/150/200/10 mg |
| *Population:* Healthy adults |
| *Dose selection:* Approved doses used for all medications |
| *Administration with regard to food:*<br>Treatment A, B, C, D: regular breakfast (533 kcal, 189 from fat)<br>Treatment E: fasted<br>Treatment F: high-fat breakfast (928 kcal, 504 from fat) |
| *Formulation:*<br>D/C/F/TAF: G001 (commercial formulation)<br>Other study medications: commercial formulations |
| *Excluded concomitant medications:* No medications are allowed except paracetamol, ibuprofen, or hormonal contraceptions, or for treatment of rash, nausea, or diarrhea. |
| *PK sampling:* Intensive sampling (17 samples) through 48 hours postdose |
| *Bioanalytical methods:* |

(b) (4)

**RESULTS**

**Demographics**

72 subjects were enrolled and all completed the study. Demographics were similar between treatment groups. Mean age was 37 years and mean BMI was 25 kg/m$^2$. Subjects were 54% male, 96% white, and 3% Hispanic.

**Protocol Deviations**

Four major deviations were reported, all due to violations of exclusion criteria (elevated bilirubin [n=1], elevated total pancreatic amylase [n=2], smoked cigarettes between screening and first treatment [n=1]).

**Concomitant medications**

There were no reported use of prohibited concomitant medications.

**Pharmacokinetics**

Exposures of analytes in the test and reference treatments were similar, with 90% confidence intervals of $C_{max}$ and AUC ratios within 0.8-1.25, with the exception of lower $C_{max}$ and AUC of TAF from D/C/F/TAF vs E/C/F/TAF and 90% CI of the TAF $C_{max}$ ratio outside 0.8-1.25 for D/C/F/TAF vs single agent TAF (Table 42).

**Table 42.** Relative bioavailability of D/C/F/TAF vs E/C/F/TAF and vs single agents.

| Analyte | D/C/F/TAF (test) vs E/C/F/TAF (reference) | | D/C/F/TAF (test) vs single agent (reference) | |
|---|---|---|---|---|
| | $C_{max}$ | AUC | $C_{max}$ | AUC |
| DRV | Not applicable | | 1.04 (0.97, 1.12) | 1.03 (0.97, 1.09) |
| COBI | Not measured | | 0.92 (0.88, 0.97) | 0.94 (0.90, 0.99) |
| FTC | 0.94 (0.88, 1.01) | 0.98 (0.96, 1.00) | 0.92 (0.84, 1.01) | 1.00 (0.97, 1.03) |
| TAF | 0.80 (0.64, 0.99) | 0.70 (0.63, 0.78) | 0.91 (0.72, 1.17) | 1.07 (0.93, 1.23) |

Values are least squared means (90% confidence interval).

In the presence of a high-fat meal relative to fasting, DRV and COBI $C_{max}$ and AUC were higher, and FTC and TAF $C_{max}$ were lower (Table 43).

**Table 43.** The effect of food (high-fat meal/fasting) on the PK of the components of D/C/F/TAF.

| | Darunavir | Cobicistat | Emtricitabine | TAF |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| $AUC_{last}$ LSmean ratio, 90% CI | 1.52 (1.43, 1.76) | 1.41 (1.02, 1.96) | 1.00 (0.96, 1.04) | 1.12 (1.01, 1.23) |
| $C_{max}$ LSmean ratio, 90% CI | 1.82 (1.52, 2.14) | 1.30 (0.94, 1.80) | 0.79 (0.71, 0.89) | 0.55 (0.42, 0.71) |

Four subjects vomited during the study. PK data from one subject who vomited within twice the median $T_{max}$ for that treatment was excluded. Other subjects vomited after twice the median $T_{max}$ for the respective treatment and PK data were not excluded.

**Safety**

There were no deaths, SAEs, or subject discontinuations due to an AE.

**REVIEWER ASSESSMENT**

The study design is acceptable ☑ Yes ☐ No

**Study Conduct**

- Was bioanalytical method performance acceptable? ☑ Yes ☐ No
- Did protocol deviations affect the integrity of the study? ☐ Yes ☑ No
- Did use of prohibited concomitant medications affect the integrity of the study? ☐ Yes ☑ No

**Study Results**

Are the study results acceptable as reported by the sponsor? ☑ Yes ☐ No

**Labeling**

Food effect results from this study are in section 12.3 of labeling. Also, this study was included in the DRV and TAF popPK models. The popPK modeling underlies labeling statements in section 12.3 regarding the impact of demographic factors on PK.

**References**

CSR link
\\cdsesub1\evsprod\nda210455\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\tmc114fd2htx1002\csr-full-tmc114fd2htx1002.pdf

### 15.2.3. **TMC114FD2HTX1004**

| | |
|---|---|
| **Study title** | A Single-dose, Open-label, Randomized, Crossover Study to Assess the Relative Bioavailability of the Fixed-dose Combination Tablet Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) Administered Orally as a Whole Tablet, as a Split Tablet, and as Crushed Tablet in Healthy Subjects |
| **Study #** | TMC114FD2HTX1004 |
| **Study period** | 12/20/16 – 2/14/17 |

| **STUDY SUMMARY (As Reported by the Applicant)** |
|---|
| **OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS** |
| *Objectives:*<br>Primary: relative BA of DRV, COBI, FTC, and TAF for D/C/F/TAF as a whole, split, or crushed tablet |
| *Design and study schema:*<br>Single-dose, open-label, randomized, crossover study.<br>Treatment A: whole tablet<br>Treatment B: split tablet<br>Treatment C: crushed tablet<br>There was a 7 day washout period between treatments.<br>Subjects were randomized to one of six treatment sequences. |
| *Population:* Healthy adults |
| *Dose selection:* The doses of the components of D/C/F/TAF were the same as in the phase 3 study |
| *Administration with regard to food:* Fed |
| *Formulation:* G001 (commercial formulation) |
| *Excluded concomitant medications:* No medications are allowed except paracetamol, ibuprofen, or hormonal contraceptions, or for treatment of rash, nausea, or diarrhea. |
| *PK sampling:* Intensive PK (~20 samples) through 72 hours post-dose |
| *Bioanalytical methods:*<br>(b) (4) |
| **RESULTS** |
| **Demographics**<br>30 subjects were enrolled and 29 completed the study. Subjects were 60% female, 87% white, and 17% Hispanic. Mean age was 37 years and mean BMI was 27 $kg/m^2$. |
| **Protocol Deviations**<br>No major deviations were reported. |

| |
|---|
| **Concomitant medications**<br>There was no reported use of prohibited concomitant medications. |
| **Pharmacokinetics**<br>Exposures of DRV, COBI, and FTC were similar between whole, split, and crushed tablet (90% confidence intervals of $C_{max}$ and AUC ratios were within 0.8-1.25). After administration of a split vs whole tablet, TAF AUC was similar but the lower bound of TAF $C_{max}$ ratio was <0.8 (Cmax ratio [90% CI]: 0.89 [0.75, 1.07]). After administration of a crushed vs whole tablet, TAF $C_{max}$ and AUC were lower (Cmax and AUC ratios [90% CI] of 0.71 [0.59, 0.86] and 0.81 [0.75, 0.88]). |
| **Safety**<br>There were no deaths or SAEs during the study. One subject discontinued the study due to a grade 4 laboratory abnormality of asymptomatic increased lipase. |

| **REVIEWER ASSESSMENT** | |
|---|---|
| The study design is acceptable ☑ Yes ☐ No | |
| **Study Conduct** | |
| ▪ Was bioanalytical method performance acceptable? | ☑ Yes ☐ No |
| ▪ Did protocol deviations affect the integrity of the study? | ☐ Yes ☑ No |
| ▪ Did use of prohibited concomitant medications affect the integrity of the study? | ☐ Yes ☑ No |
| **Study Results**<br>Are the study results acceptable as reported by the sponsor? ☑ Yes ☐ No | |
| **Labeling Recommendations**<br>We agree with proposed labeling which states in section 2 that the D/C/F/TAF tablet can be split. | |
| **References**<br>CSR link<br>\\cdsesub1\evsprod\nda210455\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\tmc114fd2htx1004\csr-full-tmc114fd2htx1004.pdf | |

### 15.2.4. **GS-US-299-0102**

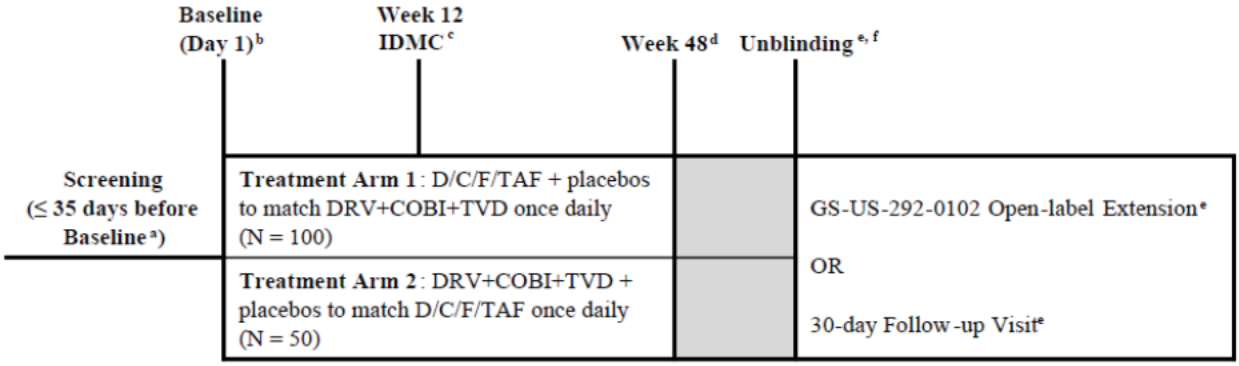
| | |
|---|---|
| **Study title** | A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Darunavir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen Versus Cobicistat-boosted Darunavir plus Emtricitabine/Tenofovir Disoproxil Fumarate Fixed Dose Combination in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults |
| **Study #** | GS-US-299-0102 |
| **Study period** | 4/16/12 – 2/19/14 |

**STUDY SUMMARY (As Reported by the Applicant)**

**OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS**

*Objectives:*
Primary: efficacy at week 24
Secondary: efficacy at week 48, safety, tolerability

*Design and study schema:*
Phase 2, randomized, double-blinded study.
Randomization stratified by HIV RNA (≤100,000 vs >100,000) and race (black vs non-black) at screening.




*Population:* HIV-infected treatment-naïve adults

*Dose selection:* Approved doses of DRV, COBI, FTC, TAF, and TDF were used

*Administration with regard to food:* Subjects were instructed to take study medication with food

*Formulation:*
D/C/F/TAF: Phase 2 formulation
DRV, COBI, FTC/TDF: commercial formulations

*Excluded concomitant medications:* Alfuzosin, modafinil, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, astemizole, terfenadfine, rifampin, rifapentine, rifabutin, pimozide, bepridil, systemic corticosteroids except <1 week prednisone burst, ergot derivatives, cisapride, St. John's Wort, echinacea, simvastatin, lovastatin, cerivastatin, midazolam or triazolam except for one-time procedures

*PK sampling:*
Sparse PK in all subjects: anytime pre- or post-dose at the end of weeks 2, 4, 12, 16, 32, and 40
Observed dosing followed by 20-24 hour post-dose PK sample: weeks 8, 24, and 48
PK substudy: week 4 or 8 intensive PK (14 samples through 24 hours post-dose)

*Bioanalytical methods:*
(b) (4)

**RESULTS**

**Demographics**
153 subjects were randomized and 126 subjects completed the study. The most common reason for discontinuation was loss to follow-up (n=14). Demographics were similar between treatment arms. Mean age was 35 years and mean BMI was 26 kg/m$^2$. Subjects were 93% male, 60% white, and 21% Hispanic.

**Protocol Deviations**
52 important deviations were reported for 35 subjects. The most common deviation was incorrect dispensing or dosing of study drug (n=40 deviations). This category of deviation included <70% compliance, incorrect dispensing of study drug, temperature not recorded at site of study drug storage, overdose of study drug, and taking study drug past expiration date.

**Concomitant medications**
Three subjects reported use of prohibited concomitant medications (echinacea single dose, dexamethasone single dose, echinacea for nine days).

**Adherence**
Median adherence calculated from pill counts was >98% in both arms of the study.

**Pharmacokinetics**
The intensive PK substudy enrolled 21 subjects in the D/C/F/TAF arm and 14 in the D/C/F/TDF arm. All components were measured in the D/C/F/TAF arm and only TFV and TFV-DP were measured in the D/C/F/TDF arm. AUC ratios (90% CI) (D/C/F/TAF / D/C/F/TDF) for TFV and TFV-DP were 0.09 (0.07, 0.11) and 6.52 (2.68, 15.9), respectively; however, note that TFV-DP bioanalytical methods were not validated. PK parameters of DRV, COBI, and FTC were similar in comparison to other products (Table 44). See section 10 (page 92) of the CSR for concentration-time profiles and PK parameters.

**Table 44.** DRV, COBI, and FTC AUC from D/C/F/TAF vs other products.

| Product | Analyte | $AUC_{24h}$ (ng*h/mL) |
|---|---|---|
| D/C/F/TAF | DRV | 99302 |
| DRV/c | | 100152 |
| D/C/F/TAF | COBI | 8744 |

| | | |
|---|---|---|
| E/C/F/TAF | | 9500 |
| D/C/F/TAF | FTC | 11918 |
| E/C/F/TAF | | 11700 |

Doses of DRV, COBI, and FTC are the same between products.

**Efficacy**

Virologic response rates in the D/C/F/TAF and D/C/F/TDF arms were 74.8% and 74.0%, respectively. D/C/F/TAF was determined to be noninferior to D/C/F/TDF.

**Safety**

There were no deaths during the study. Seven SAEs were reported (five in the D/C/F/TAF arm, two in the D/C/F/TDF arm). Four subjects (two in each arm) discontinued due to an AE.

**REVIEWER ASSESSMENT**

The study design is acceptable ☑ Yes ☐ No

**Study Conduct**

- Was bioanalytical method performance acceptable? ☑ Yes ☐ No
- Did protocol deviations affect the integrity of the study? ☐ Yes ☑ No
- Did use of prohibited concomitant medications affect the integrity of the study? ☐ Yes ☑ No

**Study Results**

Are the study results acceptable as reported by the sponsor? ☑ Yes ☐ No

**Discussion**

Bioanalytical methods were overall acceptable with the exception of TFV-DP, where bioanalytical methods were not validated. During FTC sample analysis, the CV% of the low QC (15 ng/mL) was >20%, which exceeds acceptable variability. However, FTC mean $C_{24h}$ was 93 ng/mL and thus the variability at the low QC has no impact.

There were a number of protocol deviations with potential impact on the study. However, PK results were in line with prior studies of the components of D/C/F/TAF, suggesting no major impact of the deviations on the study.

**Labeling**

Intensive PK parameters measured in this study were included in section 12.3 of labeling. Also, this study was included in the DRV and TAF popPK models. The popPK modeling underlies labeling statements in section 12.3 regarding the impact of demographic factors on PK.

**References**

CSR link
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### 15.2.5. **TMC114FD2HTX3001**

| | |
|---|---|
| **Study title** | A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects |
| **Study #** | TMC114FD2HTX3001 |
| **Study period** | 7/6/15 – 3/13/2017 (week 48 primary analysis date) |

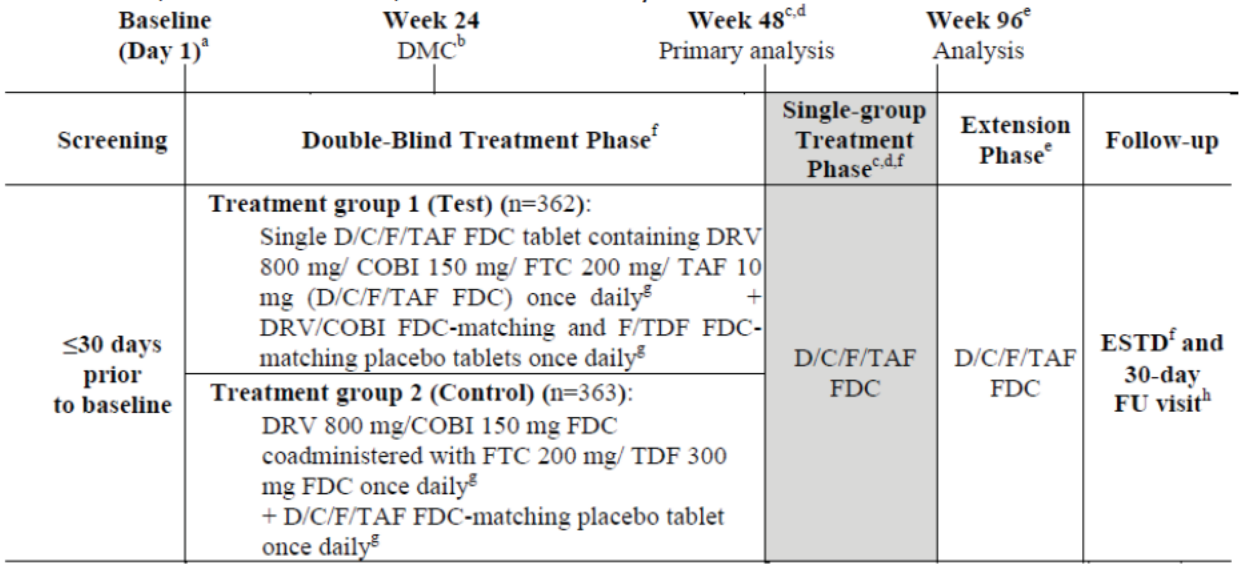
**STUDY SUMMARY (As Reported by the Applicant)**

**OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS**

*Objectives:*
Primary: noninferiority in efficacy of D/C/F/TAF vs DRV/c + FTC/TDF
Secondary: superiority of D/C/F/TAF vs DRV/c + FTC/TDF, CD4+ counts, safety, renal biomarkers, resistance, PK of DRV and TAF, bone biomarkers

*Rationale:* Registrational trial to determine if D/C/F/TAF is safe and effective when compared to approved drugs DRV/c + FTC/TDF

*Design and study schema:*
Randomized, active-controlled, double-blind study




*Population:* HIV-infected treatment-naïve adults

*Dose selection:* Approved doses of DRV, COBI, FTC, and TAF were used. However, because TAF exposure is not increased in the presence of DRV/c and is increased in the presence of EVG/c, exposures of TAF from D/C/F/TAF are expected to be lower than exposures from TAF from E/C/F/TAF.

| |
|---|
| *Administration with regard to food:* Take with food |
| *Formulation:* G001 (intended commercial formulation) |
| *Excluded concomitant medications:* Alfuzosin, modafinil, ranolazine, amiodarone, quinidine, dronedarone, systemic lidocaine used as an anti-arrhythmic, rivaroxaban, apixaban, dabigatran, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, colchicine in patients with renal or hepatic impairment, telaprevir, boceprevir, simeprevir, ombitasvir, paritaprevir, ritonavir, dasabuvir, astemizole, terfenadfine, rifampin, rifapentine, rifabutin, everolimus, pimozide, quetiapine, sertindole, bepridil, systemic corticosteroids except <1 week prednisone burst, bosentan, ergot derivatives, cisapride, St. John's Wort, echinacea, simvastatin, lovastatin, salmeterol, avanafil, other PDE-5 inhibitors for pulmonary hypertension, ticagrelor, midazolam or triazolam except for one-time procedures |
| *PK sampling:*<br>Weeks 2, 4, 12, 24, 48: 30 minutes to 4 hours postdose<br>Week 8 and 36: Two samples collected with at least 2.5 hours between sampling, with the first sample taken 1-4 hours postdose |
| *Bioanalytical methods:*<br>(b) (4) |
| **RESULTS** |
| **Notes**<br>Our focus for this study review was on PK data from the D/C/F/TAF arm included in the DRV and TAF popPK models. For this reason, most results below are summarized only for the D/C/F/TAF arm. |
| **Demographics**<br>362 subjects were enrolled in the D/C/F/TAF arm; 23 discontinued and 339 are ongoing. In the D/C/F/TAF arm, subjects were 88% male, 83% white; mean age was 36 years and mean BMI was 25 $kg/m^2$. |
| **Protocol Deviations**<br>In the D/C/F/TAF arm, protocol deviations were reported for 19 (5.2%) subjects. These included not meeting inclusion/exclusion criteria or all labs not available at baseline (n=6), late SAE reporting (n=4), randomized to wrong HIV RNA stratification group (n=3), missed visits (n=2) missed dose (n=1), dispensed wrong numbered medication kit (n=1), wrong consent form version used for patient consent (n=1), and ECG done at wrong time for baseline visit (n=1). Three subjects not meeting inclusion/exclusion criteria or all labs not available at baseline were excluded from the per protocol analysis. |
| **Concomitant medications**<br>In our analysis, one subject in the D/C/F/TAF arm used a prohibited medication (quetiapine, used from day 338 through 367). |
| **Adherence**<br>Adherence was assessed via pill counts. Cumulative treatment adherence through week 48 /was >95% in 88% of D/C/F/TAF subjects and 88% of control subjects. |

| |
|---|
| **Pharmacokinetics and pharmacodynamics**<br>The applicant reports similar DRV and TAF PK in comparison to prior studies, no differences in DRV or TAF PK parameters by subgroups (age, eGFR, adherence), and no associations between quartiles of DRV or TAF PK parameters and virologic response rate or safety (selected AEs or laboratory parameters). |
| **Efficacy**<br>Virologic response rates were 91.4% in the D/C/F/TAF group and 88.4% in the control group. D/C/F/TAF was noninferior to the control treatment. No subjects developed resistance to DRV or TAF; one subject developed resistance to FTC. |
| **Safety**<br>One subject in the control group died of sclerosing cholangitis on day 158 of the study.<br>Serious adverse events were reported in 17 (4.7%) subjects in the D/C/F/TAF arm and 21 (5.8%) in the control arm. The most common SAEs were infections, injuries, and neoplasms.<br>Seven subjects (1.9%) in the D/C/F/TAF arm and 16 (4.4%) in the control arm had AEs leading to discontinuation. These were mainly skin-related AEs (6/7 in the D/C/F/TAF arm and 10/16 in the control arm). |

| **REVIEWER ASSESSMENT** | |
|---|---|
| The study design is acceptable ☑ Yes ☐ No | |
| **Study Conduct** | |
| ▪ Was bioanalytical method performance acceptable? | ☑ Yes ☐ No |
| ▪ Did protocol deviations affect the integrity of the study? | ☐ Yes ☑ No |
| ▪ Did use of prohibited concomitant medications affect the integrity of the study? | ☐ Yes ☑ No |
| **Study Results** | |
| Are the study results acceptable as reported by the sponsor? ☑ Yes ☐ No | |
| **Labeling**<br>This study was included in the DRV popPK model. The popPK modeling underlies labeling statements in section 12.3 regarding the impact of demographic factors on PK. | |
| **References**<br>CSR link<br>\\cdsesub1\evsprod\nda210455\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv-1\5351-stud-rep-contr\tmc114fd2htx3001\csr-full-tmc114fd2htx3001.pdf | |

### 15.2.6. **TMC114IFD3013**

| | |
|---|---|
| **Study title** | A Phase 3, randomized, active-controlled, open-label study to evaluate the efficacy, safety and tolerability of switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects |
| **Study #** | TMC114IFD3013 |
| **Study period** | 4/1/15 – 2/24/17 (date of week 48 primary analysis) |

**STUDY SUMMARY (As Reported by the Applicant)**

**OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS**

*Objectives:*
Primary: noninferiority in efficacy of D/C/F/TAF vs bPI + FTC/TDF
Secondary: superiority of D/C/F/TAF vs DRV/c + FTC/TDF, virologic outcomes, CD4+ counts, safety, renal biomarkers, resistance, PK of DRV, adherence, bone biomarkers

*Rationale:* Registrational trial to determine if switching to D/C/F/TAF is safe and effective compared to subjects remaining on a regimen consisting of a bPI plus FTC/TDF

*Design and study schema:*

| Baseline (Day 1)[a] | Week 24 | Week 48[b] Primary analysis | Week 96 or beyond[b] |
|---|---|---|---|
| **Screening** | **Treatment phase[c]** | **Extension phase[b,c]** | **Follow-up** |
| ≤30 days prior to baseline | **Treatment group 1 (Test)**: Single FDC tablet containing DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (D/C/F/TAF tablet) once daily[d] (n=763) | D/C/F/TAF[d] | ESTD[c] and/or 30-day FU visit[f] |
| | **Treatment group 2 (Control)**: Continue current bPI combined with F/TDF only[e] (n=378) | | |

*Population:* Virologically suppressed adults on a bPI + FTC/TDF regimen

*Dose selection:* Approved doses of DRV, COBI, FTC, and TAF were used. However, because TAF exposure is not increased in the presence of DRV/c and is increased in the presence of EVG/c, exposures of TAF 10 mg from D/C/F/TAF are expected to be lower than exposures from TAF 10 mg from E/C/F/TAF.

*Administration with regard to food:* Take with food

*Formulation:* G001 (intended commercial formulation)

*Excluded concomitant medications:* Alfuzosin, modafinil, ranolazine, amiodarone, quinidine, dronedarone, systemic lidocaine used as an anti-arrhythmic, rivaroxaban, apixaban, dabigatran, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, colchicine in patients with renal or hepatic impairment, telaprevir, boceprevir, simeprevir, ombitasvir, paritaprevir, ritonavir,

| |
|---|
| dasabuvir, astemizole, terfenadfine, rifampin, rifapentine, rifabutin, everolimus, pimozide, quetiapine, sertindole, bepridil, systemic corticosteroids except <1 week prednisone burst, bosentan, ergot derivatives, cisapride, St. John's Wort, echinacea, simvastatin, lovastatin, salmeterol, avanafil, other PDE-5 inhibitors for pulmonary hypertension, ticagrelor, midazolam or triazolam except for one-time procedures |
| *PK sampling:* PK samples were collected in the D/C/F/TAF only on weeks 2, 4, 8, 12, 24, 36, 48. Samples were collected at least 15 minutes postdose if the visit time concodes with regular dosing time, otherwise samples were taken at any time during the visit. |
| *Bioanalytical methods:* (b) (4) |
| **RESULTS** |
| **Notes**<br>Our focus for this study review was on PK data from the D/C/F/TAF arm included in the DRV popPK model. For this reason, most results below are summarized only for the D/C/F/TAF arm. |
| **Demographics**<br>763 subjects were enrolled in the D/C/F/TAF arm; 34 discontinued and 729 are ongoing. In the D/C/F/TAF arm, subjects were 82% male, 76% white; mean age was 45 years and mean BMI was 26 $kg/m^2$. |
| **Protocol Deviations**<br>In the D/C/F/TAF arm, major protocol deviations were reported for 40 (5.2%) subjects. The most common reasons were entered but did not satisfy criteria (n=13), received wrong treatment or dose (n=4), and used disallowed medication (n=6). |
| **Concomitant medications**<br>In our analysis, 16 subjects in the D/C/F/TAF arm used disallowed concomitant medications during the treatment phase. These included systemic glucocorticoids for >1 week (n=11 subjects), alfuzosin (n=2), amiodarone (n=1), rifabutin (n=1), avanafil (n=1), and quetiapine (n=1). |
| **Adherence**<br>Adherence was assessed via pill counts. Cumulative treatment adherence through week 48 was >95% in 92% of D/C/F/TAF subjects and 85% of control subjects. |
| **Pharmacokinetics**<br>The applicant reports similar DRV and TAF PK in comparison to prior studies, no differences in DRV or TAF PK parameters by subgroups (age, eGFR, hepatitis B/C co-infection, adherence), and no associations between quartiles of DRV or TAF PK parameters and virologic response rate or safety (selected AEs or laboratory parameters). |
| **Efficacy**<br>The virologic rebound rates were 2.5% in the D/C/F/TAF group and 2.1% in the control group. D/C/F/TAF was noninferior to the control treatment. |
| **Safety**<br>No deaths occurred. SAEs were reported in 25 (4.6%) D/C/F/TAF subjects and 18 (4.8%) control subjects. The most common SAEs in both arms were infections and GI disorders. AEs leading to study discontinuation were reported for 11 (1.4%) D/C/F/TAF subjects and 5 (1.3%) control |

| |
|---|
| subjects. The most common AEs leading to discontinuation were GI disorders in the D/C/F/TAF arm (n=3) and renal and urinary disorders in the control arm (n=2). |

| **REVIEWER ASSESSMENT** | |
|---|---|
| The study design is acceptable ☑ Yes ☐ No | |
| **Study Conduct** | |
| ▪ Was bioanalytical method performance acceptable? | ☑ Yes ☐ No |
| ▪ Did protocol deviations affect the integrity of the study? | ☐ Yes ☑ No |
| ▪ Did use of prohibited concomitant medications affect the integrity of the study? | ☐ Yes ☑ No |
| **Study Results**<br>Are the study results acceptable as reported by the sponsor? ☑ Yes ☐ No | |
| **Discussion**<br>~70 COBI samples were not measured within the validated duration of stability. The results of the study are overall acceptable because only DRV concentrations from this study were included in the popPK model and thus labeling. COBI concentrations reported in labeling are from the PK substudy in the Phase 2 study. | |
| **Labeling**<br>This study was included in the DRV popPK model. The popPK modeling underlies labeling statements in section 12.3 regarding the impact of demographic factors on PK. | |
| **References**<br>CSR link<br>\\cdsesub1\evsprod\nda210455\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv-1\5351-stud-rep-contr\tmc114ifd3013\csr-full-tmc114ifd3013.pdf | |

### 15.2.7. DRV Population PK

| | |
|---|---|
| **Study title** | 48 Week Exposure Metric Estimation for Darunavir (TMC114) from Studies TMC114FD2HTX3001 and TMC114IFD3013 |
| **Report date** | 7/19/17 |

**STUDY SUMMARY (As Reported by the Applicant)**

*Objectives:* Characterize DRV PK from phase 3 D/C/F/TAF studies using a previously developed DRV popPK model and evaluate covariates

*Methods:* Nonlinear mixed effects modeling using NONMEM software

**RESULTS**

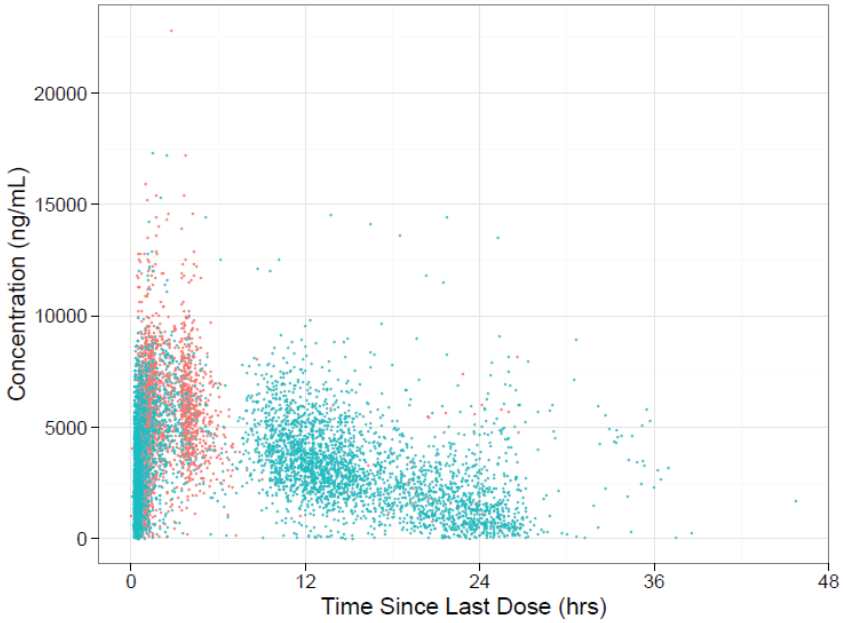
**Data included in the model**

Studies TMC114FD2HTX3001 (study 3001) and TMC114IFD3013 (study 3013) were included in the model for exposure estimation. Both studies were in HIV-infected adults, used the commercial formulation and dose, collected sparse PK, and used the same DRV assay. 1103 subjects were included in the model and were predominantly white and male (Table 45). Following exclusion of 87 samples for various reasons (including 15 BLQ samples), 8037 samples were included in the model. Samples were collected throughout the 24 hour dosing interval (Figure 14). Covariates evaluated included age, weight, CrCL, gender, and race on variability in CL and V.

**Table 45.** Demographics.

| | Age (years) | Weight (kg) | CrCL (mL/min) | AAG (mg/dL) | Sex | Race |
|---|---|---|---|---|---|---|
| N | 1103 | 1103 | 1103 | 1103 | Female: 179 (16.2%) | Asian: 21 (1.9%) |
| Mean | 42.3 | 79 | 113 | 83.9 | Male: 924 (83.8%) | Black: 187 (17%) |
| SD | 11.6 | 16.5 | 31.2 | 22.3 | | Hispanic: 161 (14.6%) |
| CV% | 27.3 | 20.9 | 27.7 | 26.6 | | Other: 16 (1.5%) |
| Median | 42 | 76.5 | 109 | 81 | | White: 718 (65.1%) |
| Min | 19 | 40.5 | 47.4 | 39.7 | | |
| Max | 75 | 204 | 314 | 201 | | |

**Figure 14.** DRV concentration-time profile in D/C/F/TAF phase 3 studies.

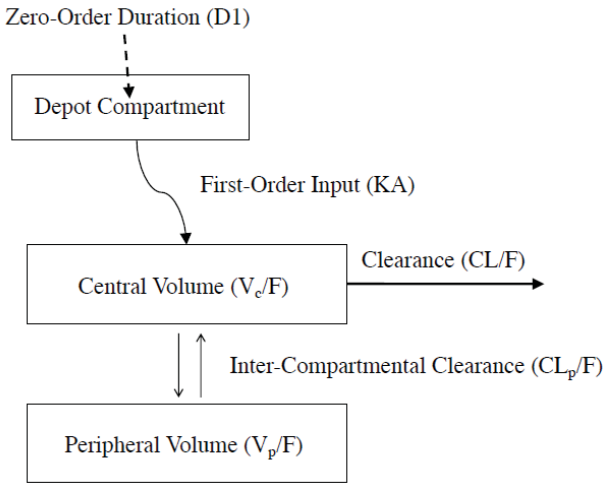



Circles = individual observations, red = TMC114FD2HTX3001, blue = TMC114IFD3013.

**Model development**

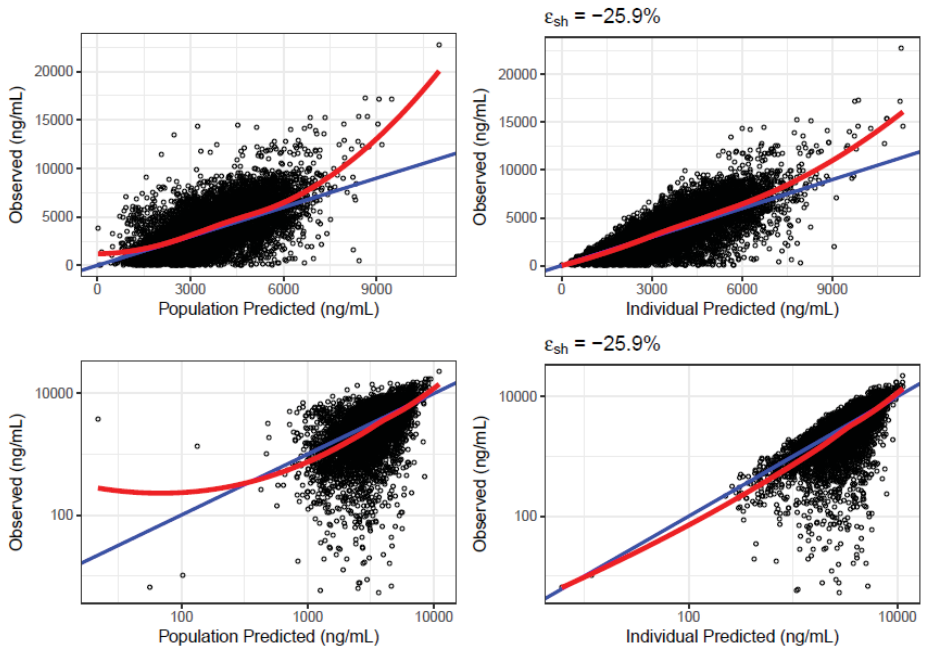
The 2-compartment model was developed from prior DRV/r studies with intensive sampling and updated with richly sampled PK data from a phase 3 DRV/c study (Figure 15). Fixed parameters included the effect of total daily dose on CL, the effect of AAG concentration on CL, relative bioavailability, and between-subject variability on peripheral volume.

**Figure 15.** DRV model structure.



The model was updated by re-estimating parameters using the dataset consisting of studies 3001 and 3013. As assessed by goodness-of-fit plots, visual predictive check, and individual subject observed vs predicted concentration-time profiles, performance of the updated model was acceptable (Figure 16; also see figures 16-19 in the study report and individual subject profiles in NDA 210455 SDN 21). Several parameters differed between the prior and updated model (Table 46). The updated model included a parameter for the effect of weight on CL.

**Figure 16.** Observed versus predicted DRV concentrations.




The solid blue lines represent the line of unity, the solid red lines represent the trend in the data (Loess smooth), and $\varepsilon_{sh}$ shows shrinkage for the residual variability.

**Table 46.** Prior and updated model parameters.

| Parameter | Updated Model Estimate (CV%) | Prior Model Estimate (CV%) |
|---|---|---|
| *Apparent clearance (CL/F, L/hr) | 44.05 (1.13) | 51.6 (3.4) |
| Effect of TDD on CL/F | 0.388 FIX | 0.388 FIX |
| Effect of AAG on CL/F (dL/mg) | 0.0304 FIX | 0.0304 FIX |
| Exponent of WT on CL/F | 0.296 (16.2) | – |
| Apparent volume of distribution for the central compartment ($V_c$/F, L) | 88.3 (4.2) | 35.6 (19.9) |
| Apparent inter-compartmental clearance ($CL_p$/F, L/hr) | 24.0 FIX | 24.0 (19.4) |
| Apparent volume of distribution for the peripheral compartment ($V_p$/F, L) | 90.0 FIX | 90.0 (10.4) |
| First-order absorption rate constant (KA, $hr^{-1}$) | 0.393 FIX | 0.393 (18.5) |
| Relative bioavailability ($F_{REL}$) | 1.18 FIX | 1.18 FIX |
| Duration of zero-order input into the depot compartment (D1, hr) | 0.289 (10.4) | 1.49 (11.1) |
| Between-subject variability on CL/F (CV%) | 23.0 (7.5) | 24.9 (18.3) |
| Between-subject variability on $V_c$/F (CV%) | 15.6 FIX | 15.6 (210) |
| Between-subject variability on $CL_p$/F (CV%) | 51.0 FIX | 51.0 (34.3) |
| Between-subject variability on $V_p$/F (CV%) | 55.7 FIX | 55.7 FIX |
| Between-subject variability on D1 (CV%) | 88.4 FIX | 88.4 (27.4) |
| Residual unexplained variability (Proportional RUV, CV%) | 43.2 (2.86) | 18.2 (20.5) |

CV% = percent coefficient of variation, AAG = $\alpha_1$-acid glycoprotein, TDD = total daily dose, WT = total body weight.*CL/F = $44.05 \cdot (1/(1 + 0.0304 \cdot AAG)) \cdot (TDD/1200)^{0.388} \cdot (WT/70)^{0.296}$.

**Pharmacokinetics**

Predicted PK parameters in studies 3001 and 3013, and as a function of body weight, are shown below (Table 47, Table 48). DRV PK parameters from this analysis were similar to a prior study of DRV/c (Table 49).

**Table 47.** DRV PK parameters in D/C/F/TAF phase 3 studies.

| Study | Exposure Metric | Number | Mean | SD | Percentile 2.5th | Percentile 50th | Percentile 97.5th |
|---|---|---|---|---|---|---|---|
| TMC114FD2HTX3001 | $AUC_{24h}$ (ng.hr/mL) | 2395 | 90283 | 23485 | 57115 | 86957 | 145106 |
| | $C_{0h}$ (ng/mL) | 2395 | 1989 | 880 | 797 | 1848 | 4040 |
| | $C_{ss,ave}$ (ng/mL) | 2395 | 3762 | 979 | 2380 | 3623 | 6046 |
| TMC114IFD3013 | $AUC_{24h}$ (ng.hr/mL) | 5002 | 87340 | 24724 | 50310 | 83580 | 143274 |
| | $C_{0h}$ (ng/mL) | 5002 | 1866 | 942 | 520 | 1703 | 4103 |
| | $C_{ss,ave}$ (ng/mL) | 5002 | 3639 | 1030 | 2096 | 3483 | 5970 |

Number = total number of exposure metrics reported for each study.

**Table 48.** DRV PK parameters in D/C/F/TAF phase 3 studies as a function of weight.

| Quartile | Mean (SD) $AUC_{24h}$ (ng.hr/mL) | Mean (SD) $C_{max}$ (ng/mL) | Mean (SD) $C_{0h}$ (ng/mL) |
|---|---|---|---|
| 1st Quartile | 89861 (2484) | 5973 (97.6) | 1913 (88.6) |
| 4th Quartile | 77484 (2654) | 5503 (98.4) | 1484 (88.7) |

$AUC_{24h}$ = area under the plasma concentration-time curve from time of administration to 24 hours, $C_{max}$ = maximum plasma concentration, $C_{0h}$ = trough concentration, SD – standard deviation, 1st quartile = WT < 67.8 kg, 4th quartile = WT > 87.5 kg.

**Table 49.** DRV popPK parameters from D/C/F/TAF vs DRV/c.

| Analysis or study | Mean $AUC_{24h}$ (ng*h/mL) ± SD | Mean $C_{0h}$ (ng/mL) ± SD |
|---|---|---|

| | | |
|---|---|---|
| D/C/F/TAF popPK analysis of study TMC114FD2HTX3001 | 90283 ± 23485 | 1989 ± 880 |
| DRV/c study GS-US-216-0130 | 100152 ± 32042 | 2043 ± 1257 |

PK parameters from DRV/c study GS-US-216-0130 obtained from PREZCOBIX labeling.

**REVIEWER ASSESSMENT**

Study conduct for studies included in the model is acceptable ☑ Yes ☐ No

The model is acceptable ☑ Yes ☐ No

**Labeling**

DRV popPK parameters are included in section 12.3. Also, we agree with labeling statements from this analysis regarding the impact of demographic factors on DRV PK (no impact of age >65 years, gender, or race).

**Relevant links within the submission**

CSR
\\cdsesub1\evsprod\nda210455\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\dcftaf-phase3-drv-poppk\dcftaf-phase3-drv-poppk.pdf

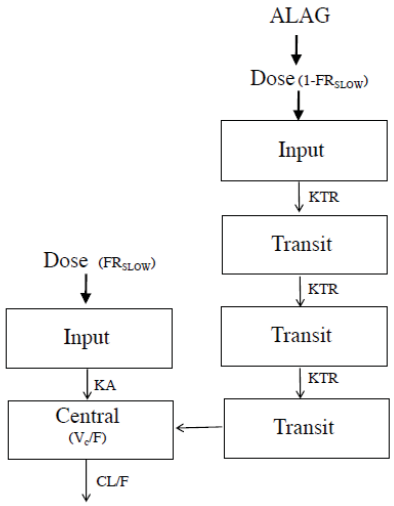
### 15.2.8. TAF Population PK

| | |
|---|---|
| **Title** | Development of a Population Pharmacokinetic Model for Tenofovir Alafenamide (TAF) & 48 Week Exposure Metric Estimation from Study TMC114FD2HTX3001 |
| **Report date** | 7/19/2017 |

| **STUDY SUMMARY (As Reported by the Applicant)** |
|---|
| **METHODS** |
| *Objectives:* Characterize the PK of TAF in phase 1-3 studies |
| *Methods:* Nonlinear mixed effects modeling using NONMEM software |
| **RESULTS** |
| **Data included in the model**<br>TAF PK data from two phase 1 intensive PK studies (TMC114FD2HTX1001, TMC114FD2HTX1002) and one phase 2 study that evaluated intensive and sparse PK (GS-US-299-0102) were used for model building. Due to PK differences, TAF PK from E/C/F/TAF and TAF PK collected in the fasted state or after a high fat meal were excluded. BLQ samples were excluded. After data exclusions, the dataset contained 2319 samples from 246 subjects.<br><br>Data from phase 3 study TMC114FD2HTX3001 (sparse PK) was used for model refinement. |
| **Model development**<br>Model development was stepwise, with model refinement occuring as data were added to the dataset. Model parameters estimated in earlier stages were fixed in subsequent stages. For example, one of 14 model parameters was fixed in the TAF base model and 16 of 17 parameters were fixed in the final model (Table 50). The initial dataset contained intensive PK data from healthy volunteers from one occasion; then multiple occasion data was added. Next intensive and then sparse PK data from HIV-infected subjects were added. Covariate analysis and evaluation of BLQ data was then done. Finally the model was refined after including sparse PK data from Phase 3 study 3001.<br><br>The final model was a one compartment model with dual input (slow and fast). Absorption by the slow pathway was first order and absorption via the fast pathway was described using lag time and transit compartments (Figure 17). A mixture model was implemented for lag time (yes or no) by occasion (two occasions), for a total of four subpopulations. After including BQL samples and using the M3 method for estimation (which accounts for BLQ samples), parameter estimates were similar as when BQL samples were excluded.<br><br>Several demographic (age, weight, sex, race, study population), laboratory (creatinine clearance, cystatin clearance, ALT, AST, bilirubin, albumin, AAG), and other factors (fed status, formulation) were evaluated. The final model included covariates for lean body weight and alpha 1 acid glycoprotein concentration on clearance. Between subject variability parameters |

were included for CL, V, and absorption parameters, and between occasion variability in absorption lag time (Table 50).

**Figure 17.** Structural model.




Source: study report page 9.

**Table 50.** TAF final model parameter estimates.

| Parameter | Estimated Value (%SE) | |
|---|---|---|
| | Phase III Model (Step 8) | Phase I/II Model (Step 5) |
| *Apparent clearance (CL/F, L/hr) | 89.0 FIX | 89.0 (2.4) |
| Exponent for LBW on CL | 0.70 FIX | 0.70 (13.9) |
| Exponent for AAG on CL | -0.63 FIX | -0.63 (11.7) |
| Apparent central volume of distribution ($V_c$/F, L) | 36.3 FIX | 36.3 (4.7) |
| First order absorption rate constant for pathway one (KA, $hr^{-1}$) | 0.67 FIX | 0.67 FIX |
| Absorption transit rate constant for pathway two (KTR, $hr^{-1}$) | 38.3 (30.6) | 6.15 FIX |
| Fraction of dose via the slow pathway ($FR_{SLOW}$) | 0.135 FIX | 0.135 FIX |
| Probability of subpopulation one ($MIX_1$), two ($MIX_2$), or three ($MIX_3$)** | 0.21 FIX | 0.21 FIX |
| Lag-time for second pathway (ALAG, hrs) | 0 FIX | 0.57 FIX |
| Between subject variability for CL/F (%CV) | 27.0 FIX | 27.0 (10.4) |
| Between subject variability for $V_c$/F (%CV) | 37.3 FIX | 37.3 (10.0) |
| Between subject variability for KA (%CV) | 55.6 FIX | 55.6 FIX |
| Between subject variability for KTR (%CV) | 66.8 FIX | 66.8 FIX |
| Between subject variability for $FR_{SLOW}$ (%CV) | 78.9 FIX | 78.9 FIX |
| Between occasion variability for ALAG (%CV) | NA | 66.8 FIX |
| Residual unexplained variability Rich (%CV) | NA | 45.1 (2.4) |
| Residual unexplained variability Sparse (%CV) | 75.9 FIX | 75.9 (17.5) |

BSV = between-subject variability, SE = standard error, CV% = percent coefficient of variation, LBW = lean body weight, AAG = $\alpha_1$-acid glycoprotein. *CL/F = $89.0 \cdot (LBW/55)^{0.70} \cdot (AAG/68)^{-0.63}$, **Subpopulation 4 = 0.37 [i.e. 1 - 0.21 - 0.21 - 0.21]

Source: study report page 100.

Goodness-of-fit as assessed by observed vs predicted concentrations (overall and in individual subjects) and visual predictive check were acceptable (see study report page 102, 105, and

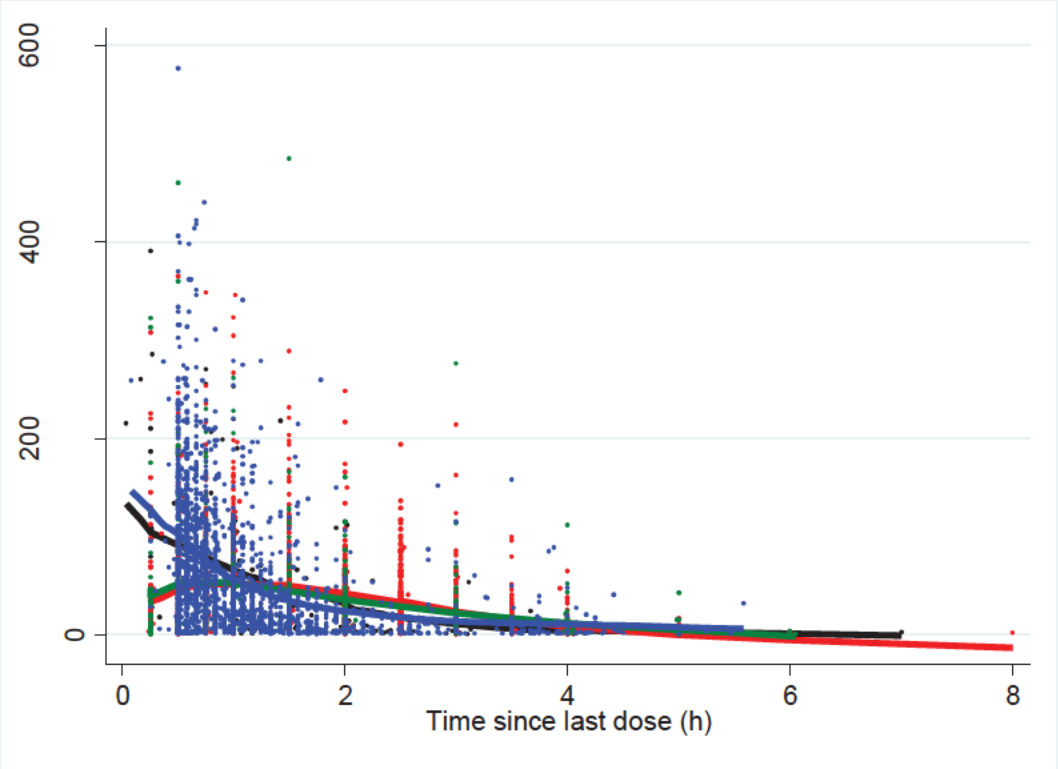
196).

**Pharmacokinetics**

**Observed TAF concentrations were highly variable and largely overlapped between studies (Figure 18, Figure 19). The need for a mixture model to account for varying absorption using lag time and differing absorption within individuals by occasion is illustrated in concentration-time profiles in**

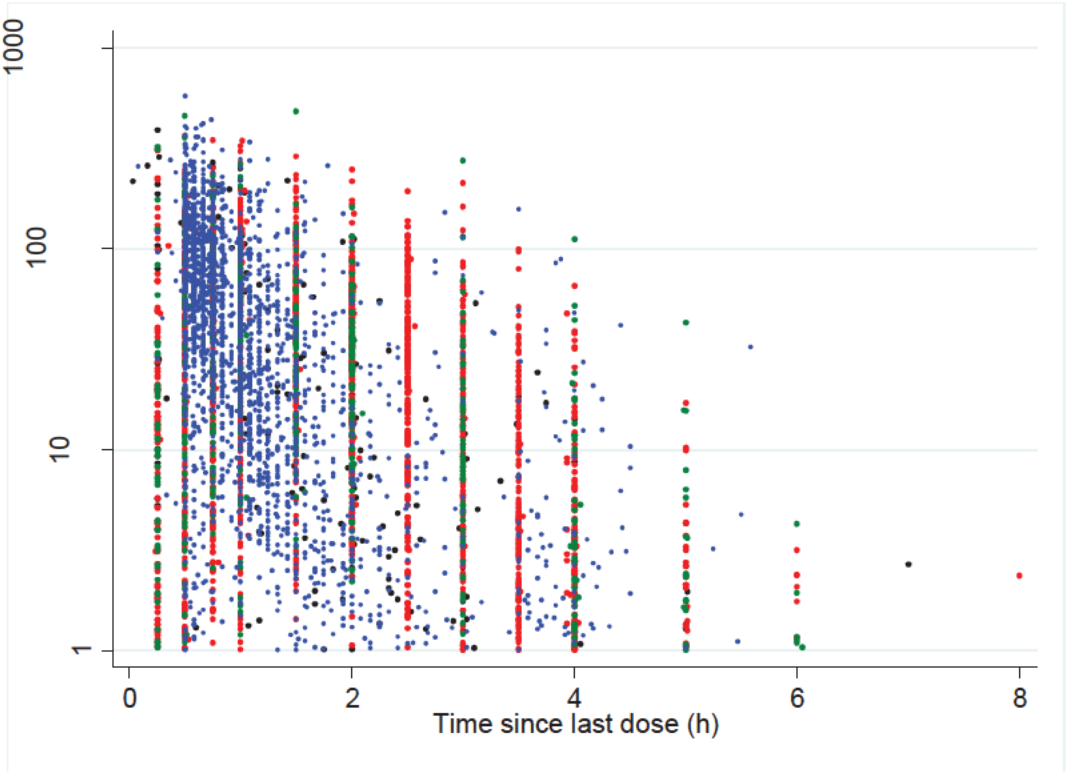
Figure 20. TAF AUC estimated using popPK in phase 3 D/C/F/TAF study TMC114FD2HTX3001 (mean = 135 ng*h/mL) was similar to TAF AUC measured from intensive PK in phase 2 D/C/F/TAF study GS-US-299-0102 (mean = 131 ng*h/mL) (Table 51).

**Figure 18.** TAF concentration-time profile for studies included in the popPK model (linear scale).



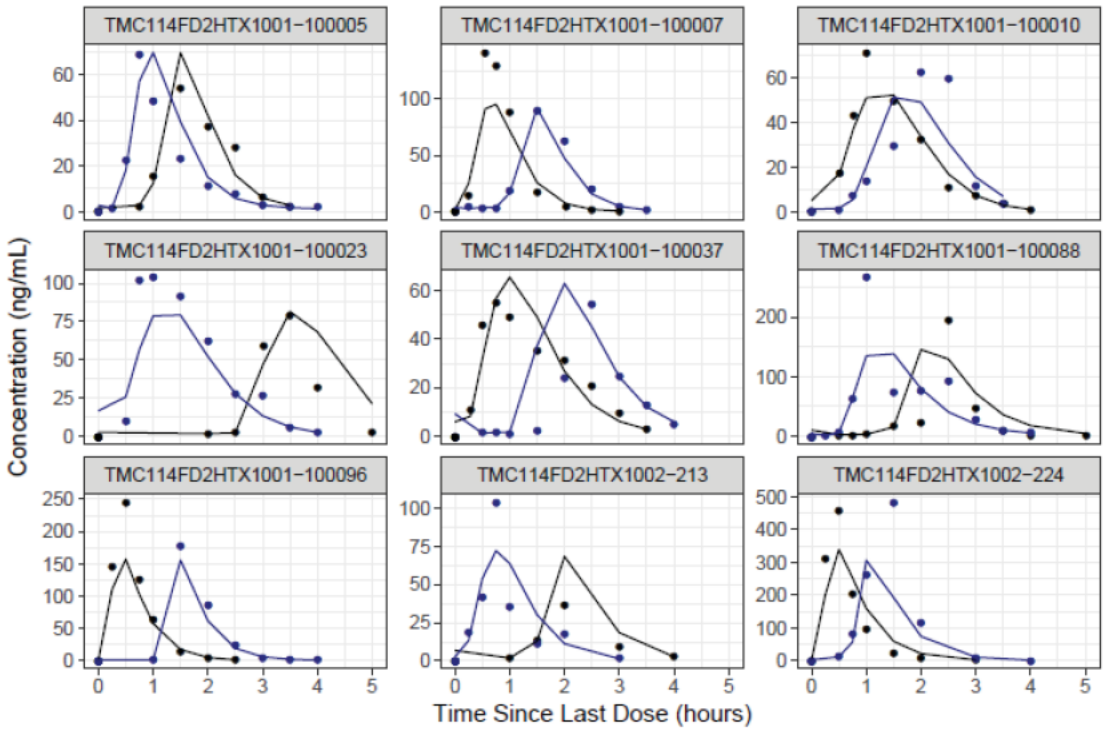

Source: plotted by reviewer. Black = phase 2 study GS-US-299-0102; red = phase 1 study TMC114FD2HTX1001; green = phase 1 study TMC114FD2HTX1002; blue = phase 3 study TMC114FD2HTX3001.

**Figure 19.** TAF concentration-time profile for studies included in the popPK model (log scale).




Source: plotted by reviewer. Black = phase 2 study GS-US-299-0102; red = phase 1 study TMC114FD2HTX1001; green = phase 1 study TMC114FD2HTX1002.

**Figure 20.** Base model individual fits - between occassion variability in absorption.




Dots = observed data, lines = individual model predictions, black = fixed dose combination, blue = single agent TAF.

Source: study report page 71.

**Table 51.** TAF exposures estimated in phase 3 D/C/F/TAF study TMC114FD2HTX3001 using popPK.

| Exposure Metric | Number | Mean | SD | Percentile | | |
|---|---|---|---|---|---|---|
| | | | | $2.5^{th}$ | $50^{th}$ | $97.5^{th}$ |
| $AUC_{24h}$ (ng.hr/mL) | 2375 | 135.2 | 44.0 | 81.69 | 125.2 | 246.3 |
| $C_{2h}$ (ng/mL) | 2375 | 12.63 | 12.4 | 0.75 | 8.30 | 46.47 |
| $C_{ss,ave}$ (ng/mL) | 2375 | 5.63 | 1.83 | 3.40 | 5.22 | 10.26 |

Source: study report page 109.

| REVIEWER ASSESSMENT |
|---|
| Study conduct for studies included in the model is acceptable ☐ Yes ☐ No |
| The model is acceptable ☑ Yes ☐ No |
| **Labeling**<br>DRV popPK parameters are included in section 12.3. Also, we agree with labeling statements from this analysis regarding the impact of demographic factors on TAF PK (no impact of age up |

| |
|---|
| to >75 years, gender, or race). |
| **Relevant links within the submission**<br>CSR<br>\\cdsesub1\evsprod\nda210455\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\tmc114fd2htx3001-taf-poppk\tmc114fd2htx3001-taf-poppk.pdf |

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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MYUNG JOO P HONG
07/17/2018