CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208215Orig1s012

Trade Name:	DESCOVY tablets
Generic or Proper Name:	emtricitabine and tenofovir alafenamide
Sponsor:	Gilead Sciences, Inc
Approval Date:	October 3, 2019
Indication:	The use in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex

CENTER FOR DRUG EVALUATION AND RESEARCH

208215Orig1s012

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 208215/S-012

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Garland Lee, PharmD
Regulatory Affairs Manager
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lee:

Please refer to your supplemental new drug application (sNDA) dated and received on April 5, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use.

This Prior Approval supplemental new drug application provides for the following changes to the DESCOVY® US Prescribing Information (USPI):

- The use of DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex
- Addition of post-marketing adverse drug reactions (ADRs) of angioedema, urticaria and rash as supported by the cumulative safety review across tenofovir alafenamide (TAF)-containing products to section 6.2, Postmarketing Experience
- To make corresponding changes to the Medication Guide

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study(ies) requirement for ages birth to adolescents weighing less than 35 kg because necessary studies are impossible or highly impracticable. This is because PrEP is intended to reduce the risk of sexually acquired HIV-1 infections, clinical trials of PrEP would be highly impracticable in a pediatric population who are not sexually mature and active or in whom the likelihood of sexual behavior is very low.

We note that you have fulfilled the pediatric study requirement for

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

this application for at-risk adolescents (weighing at least 35 kg and less than 18 years of age) for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3723-1 Conduct a randomized, comparative trial to evaluate the safety and efficacy of Descovy for pre-exposure prophylaxis (PrEP) in cisgender women and adolescent girls weighing at least 35 kg, who are at risk of sexually acquired HIV-1 infection. The trial should include a Truvada arm. The trial should employ two distinct methods to estimate the background HIV-1 incidence rate as external controls. HIV-1 incidence estimates should be based on current estimates from sites involved in recent clinical trials, cross-sectional HIV surveillance surveys, and from high quality local epidemiology data.

The timetable you submitted on September 27, 2019, states that you will conduct this clinical trial according to the following schedule:

Draft Protocol Submission:	12/2019
Final Protocol Submission:	05/2020
Trial Completion:	12/2024
Final Report Submission:	06/2025

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the clinical trial.

Submit clinical protocols to your IND 127728 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

If you have any questions, call Alicia Moruf, PharmD, MPH, Regulatory Project Manager, at 301-796-3953.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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.

/s/

JEFFREY S MURRAY
10/03/2019 01:42:37 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208215Orig1s012

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DESCOVY safely and effectively. See full prescribing information for DESCOVY.

DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION
See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of DESCOVY. Hepatic function should be monitored closely in these individuals. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

DESCOVY used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use.
Drug-resistant HIV-1 variants have been identified with use of FTC/TDF for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate DESCOVY for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed. (5.2)

----------RECENT MAJOR CHANGES----------

Boxed Warning	10/2019
Indications and Usage (1.2)	10/2019
Dosage and Administration (2.1, 2.2, 2.4, 2.5)	10/2019
Contraindications (4)	10/2019
Warnings and Precautions (5.2)	10/2019

----------INDICATIONS AND USAGE----------
HIV-1 Treatment (1.1):
DESCOVY is a two-drug combination of emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated:
- in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg.
- in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg.

HIV-1 PrEP (1.2):
DESCOVY is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating DESCOVY for HIV-1 PrEP.
Limitations of Use (1.2):
The indication does not include use of DESCOVY in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

----------DOSAGE AND ADMINISTRATION----------
- Testing: Prior to or when initiating DESCOVY, test for hepatitis B virus infection. Prior to or when initiating DESCOVY, and during use on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus. (2.1)
- HIV-1 Screening: Screen all individuals for HIV-1 infection immediately prior to initiating DESCOVY for HIV-1 PrEP and at least once every 3 months while taking DESCOVY, and upon diagnosis of any other sexually transmitted infections (STIs). (2.2)
- Recommended dosage:
  - Treatment of HIV-1 Infection: One tablet taken once daily with or without food in patients with body weight at least 25 kg. (2.3)
  - HIV-1 PrEP: One tablet taken once daily with or without food in individuals with body weight at least 35 kg. (2.4)
- Renal impairment: DESCOVY is not recommended in individuals with estimated creatinine clearance below 30 mL per minute. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 200 mg of FTC and 25 mg of TAF (3)

----------CONTRAINDICATIONS----------
DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status. (4)

----------WARNINGS AND PRECAUTIONS----------
- Comprehensive management to reduce the risk of sexually transmitted infections (STIs), including HIV-1, when DESCOVY is used for HIV-1 PrEP: Counsel on adherence to daily dosing and safer sex practices, including condoms, to reduce the risk of STIs. (5.2)
- Management to reduce the risk of acquiring HIV-1 drug resistance when DESCOVY is used for HIV-1 PrEP: refer to full prescribing information for additional detail. (5.2)
- Immune reconstitution syndrome during treatment of HIV-1 infection: May necessitate further evaluation and treatment. (5.3)
- New onset or worsening renal impairment: Assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein when initiating DESCOVY and during use on a clinically appropriate schedule in all individuals. Also assess serum phosphorus in individuals with chronic kidney disease. (5.4)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue DESCOVY in individuals who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)

----------ADVERSE REACTIONS----------
- In HIV-1 infected patients, the most common adverse reaction (incidence greater than or equal to 10%, all grades) was nausea. (6.1)
- In HIV-1 uninfected adults in a PrEP trial, the most common adverse reaction (incidence greater than or equal to 5%, all grades) was diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Consult the Full Prescribing Information prior to and during use for potential drug interactions. (7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Mothers infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV transmission. (8.2)
- Pediatrics:
  - Treatment of HIV-1 Infection: Not recommended for patients weighing less than 25 kg. (8.4)
  - HIV-1 PrEP: Not recommended for individuals weighing less than 35 kg. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescr bing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of DESCOVY.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in individuals who are infected with HBV and discontinue DESCOVY. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

DESCOVY used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of FTC/TDF for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate DESCOVY for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1 Infection

DESCOVY is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg.

DESCOVY is indicated, in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg.

1.2 HIV-1 Pre-Exposure Prophylaxis (PrEP)

DESCOVY is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating DESCOVY for HIV-1 PrEP *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.

Limitations of Use:

The indication does not include use of DESCOVY in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated *[see Clinical Studies (14.3)].*

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Use of DESCOVY for Treatment of HIV-1 Infection or for HIV-1 PrEP

Prior to or when initiating DESCOVY, test individuals for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating DESCOVY, and during use of DESCOVY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.4)].*

2.2 HIV-1 Screening for Individuals Receiving DESCOVY for HIV-1 PrEP

Screen all individuals for HIV-1 infection immediately prior to initiating DESCOVY for HIV-1 PrEP and at least once every 3 months while taking DESCOVY, and upon diagnosis of any other sexually transmitted infections (STIs) *[see Indications and Usage (1.2), Contraindications (4), and Warnings and Precautions (5.2)].*

If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection *[see Warnings and Precautions (5.2), Use in Specific Populations (8.4), and Clinical Studies (14.3)].*

2.3 Recommended Dosage for Treatment of HIV-1 Infection in Adults and Pediatric Patients Weighing at Least 25 kg

DESCOVY is a two-drug fixed dose combination product containing 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of DESCOVY for treatment of HIV-1 is one tablet taken orally once daily with or without food in adults and pediatric patients with body weight at least 25 kg and creatinine clearance greater than or equal to 30 mL per minute *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

For specific dosing recommendations for coadministered third agents, refer to their respective prescribing information *[see Drug Interactions (7)]*. The safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

2.4 Recommended Dosage for HIV-1 PrEP in Adults and Adolescents Weighing at Least 35 kg

The dosage of DESCOVY for HIV-1 PrEP is one tablet (containing 200 mg of FTC and 25 mg of TAF) once daily taken orally with or without food in HIV-1 uninfected adults and adolescents weighing at least 35 kg and with a creatinine clearance greater than or equal to 30 mL per minute, excluding individuals at risk from receptive vaginal sex *[see Clinical Pharmacology (12.3)].*

2.5 Not Recommended in Individuals with Severe Renal Impairment for Treatment of HIV-1 Infection or for HIV-1 PrEP

DESCOVY is not recommended in individuals with estimated creatinine clearance below 30 mL per minute *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

Each DESCOVY tablet contains 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets are blue, rectangular-shaped, film-coated, debossed with “GSI” on one side and “225” on the other side.

4 CONTRAINDICATIONS

DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status *[see Warnings and Precautions (5.2)].*

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Individuals with HBV Infection

All individuals should be tested for the presence of hepatitis B virus (HBV) before or when initiating DESCOVY *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in HBV-infected individuals who have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of DESCOVY. Individuals infected with HBV who discontinue DESCOVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in individuals with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. HBV-uninfected individuals should be offered vaccination.

5.2 Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When DESCOVY Is Used for HIV-1 PrEP

Use DESCOVY for HIV-1 PrEP to reduce the risk of HIV-1 infection as part of a comprehensive prevention strategy, including adherence to daily administration and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs). The time from initiation of DESCOVY for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

Risk for HIV-1 acquisition includes behavioral, biological, or epidemiologic factors including but not limited to condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high prevalence area or network.

Counsel individuals on the use of other prevention measures (e.g., consistent and correct condom use, knowledge of partner(s)' HIV-1 status, including viral suppression status, regular testing for STIs that can facilitate HIV-1 transmission). Inform uninfected individuals about and support their efforts in reducing sexual risk behavior.

Use DESCOVY to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-1 negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only DESCOVY, because DESCOVY alone does not constitute a complete regimen for HIV-1 treatment *[see Microbiology (12.4)];* therefore, care should be taken to minimize the risk of initiating or continuing DESCOVY before confirming the individual is HIV-1 negative.

- Some HIV-1 tests only detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating DESCOVY for HIV-1 PrEP, ask seronegative individuals about recent (in past month) potential exposure events (e.g., condomless sex or condom breaking during sex with a partner of unknown HIV-1 status or unknown viremic status, or a recent STI), and evaluate for current or recent signs or symptoms consistent with acute HIV-1 infection (e.g., fever, fatigue, myalgia, skin rash).
- If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.

While using DESCOVY for HIV-1 PrEP, HIV-1 testing should be repeated at least every 3 months, and upon diagnosis of any other STIs.

- If an HIV-1 test indicates possible HIV-1 infection, or if symptoms consistent with acute HIV-1 infection develop following a potential exposure event, convert the HIV-1 PrEP regimen to an HIV treatment regimen until negative infection status is confirmed using a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.

Counsel HIV-1 uninfected individuals to strictly adhere to the once daily DESCOVY dosing schedule. The effectiveness of DESCOVY in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable drug levels in a clinical trial of DESCOVY for HIV-1 PrEP. Some individuals, such as adolescents, may benefit from more frequent visits and counseling to support adherence *[see Use in Specific Populations (8.4), Microbiology (12.4), and Clinical Studies (14.3)].*

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including FTC, a component of DESCOVY. During the initial phase of combination antiretroviral treatment, HIV-1 infected patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.4 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of FTC+TAF with cobicistat (COBI) plus elvitegravir (EVG) in HIV-1 infected patients there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT). In clinical trials of FTC+TAF with EVG+COBI in treatment-naïve subjects and in virally suppressed subjects switched to FTC+TAF with EVG+COBI with estimated creatinine clearance greater than 50 mL per minute, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with FTC+TAF with EVG+COBI. In a study of virally suppressed subjects with baseline estimated creatinine clearance between 30 and 69 mL per minute treated with FTC+TAF with EVG+COBI for a median duration of 43 weeks, FTC+TAF with EVG+COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects with a baseline estimated creatinine clearance between 30 and 50 mL per minute *[see Adverse Reactions (6.1)]*. DESCOVY is not recommended in individuals with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient.

Individuals taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating DESCOVY, and during treatment with DESCOVY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus. Discontinue DESCOVY in individuals who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.5 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of DESCOVY, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with DESCOVY should be suspended in any individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbations of Hepatitis B *[see Warnings and Precautions (5.1)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.3)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.4)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.5)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug (or a drug given in various combinations with other concomitant therapy) cannot be directly compared to rates in the clinical trials of another drug (or drug given in the same or different combination therapy) and may not reflect the rates observed in practice.

<u>Adverse Reactions in Clinical Trials of FTC+TAF with EVG+COBI in Treatment-Naïve Adults with HIV-1 Infection</u>

In pooled 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, the most common adverse reaction in subjects treated with FTC+TAF with EVG+COBI (N=866) (incidence greater than or equal to 10%, all grades) was nausea (10%). In this treatment group, 0.9% of subjects discontinued FTC+TAF with EVG+COBI due to adverse events during the 48-week treatment period *[see Clinical Studies (14.2)]*. The safety profile was similar in virologically-suppressed

adults with HIV-1 infection who were switched to FTC+TAF with EVG+COBI (N=799). Antiretroviral treatment-naïve adult subjects treated with FTC+TAF with EVG+COBI experienced mean increases of 30 mg/dL of total cholesterol, 15 mg/dL of LDL cholesterol, 7 mg/dL of HDL cholesterol, and 29 mg/dL of triglycerides after 48 weeks of use.

Renal Laboratory Tests

In two 48-week trials in antiretroviral treatment-naïve HIV-1 infected adults treated with FTC+TAF with EVG+COBI (N=866) with a median baseline eGFR of 115 mL per minute, mean serum creatinine increased by 0.1 mg per dL from baseline to Week 48. Median urine protein-to-creatinine ratio (UPCR) was 44 mg per gram at baseline and at Week 48. In a 48-week trial in virologically-suppressed TDF-treated adults who switched to FTC+TAF with EVG+COBI (N=959) with a mean baseline eGFR of 112 mL per minute, mean serum creatinine was similar to baseline at Week 48; median UPCR was 61 mg per gram at baseline and 46 mg per gram at Week 48. In a 24-week trial in adults with renal impairment (baseline eGFR 30 to 69 mL per minute) who received FTC+TAF with EVG+COBI (N=248), mean serum creatinine was 1.5 mg per dL at both baseline and Week 24. Median UPCR was 161 mg per gram at baseline and 93 mg per gram at Week 24.

Bone Mineral Density Effects

In the pooled analysis of two 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA). Mean BMD decreased from baseline to Week 48 −1.30% with FTC+TAF with EVG+COBI at the lumbar spine and −0.66% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 10% of FTC+TAF with EVG+COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 7% of FTC+TAF with EVG+COBI subjects. The long-term clinical significance of these BMD changes is not known.

In 799 virologically-suppressed TDF-treated adult subjects that switched to FTC+TAF with EVG+COBI, at Week 48 mean BMD increased (1.86% lumbar spine, 1.95% total hip). BMD declines of 5% or greater at the lumbar spine were experienced by 1% of FTC+TAF with EVG+COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 1% of FTC+TAF with EVG+COBI subjects.

<u>Adverse Reactions in Clinical Trials in Pediatric Subjects with HIV-1 Infection</u>

In an open-label trial of antiretroviral treatment-naïve HIV-1 infected pediatric subjects between the ages of 12 to less than 18 years weighing at least 35 kg through 48 weeks (N=50; Cohort 1) and virologically-suppressed subjects between the ages of 6 to less than 12 years weighing at least 25 kg (N=23; Cohort 2) who received FTC+TAF with EVG+COBI through 24 weeks, with the exception of a decrease in the mean CD4+ cell count observed in cohort 2, the safety of this combination was similar to that of adults.

Bone Mineral Density Effects

Cohort 1: Treatment-naïve adolescents (12 to less than 18 years; at least 35 kg)

Among the subjects in cohort 1 receiving FTC+TAF with EVG+COBI, mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for the total body less head (TBLH). Mean changes from baseline BMD Z-scores were −0.07 for lumbar spine and −0.20 for TBLH at Week 48. One subject had significant (at least 4%) lumbar spine BMD loss at Week 48.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Among the subjects in cohort 2 receiving FTC+TAF with EVG+COBI, mean BMD increased from baseline to Week 24, +2.9% at the lumbar spine and +1.7% for TBLH. Mean changes from baseline BMD Z-scores were -0.06 for lumbar spine and -0.18 for TBLH at Week 24. Two subjects had significant (at least 4%) lumbar spine BMD loss at Week 24.

Change from Baseline in CD4+ cell counts

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Cohort 2 evaluated pediatric subjects (N=23) who were virologically-suppressed and who switched from their antiretroviral regimen to FTC+TAF with EVG+COBI. Although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in CD4+ cell count at Week 24. The mean baseline and mean change from baseline in CD4+ cell count and in CD4% from Week 2 to Week 24 are presented in Table 1. All subjects maintained their CD4+ cell counts above 400 cells/mm^3 *[see Use in Specific Populations (8.4)].*

Table 1 Mean Change in CD4+ Count and Percentage from Baseline to Week 24 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to FTC+TAF with EVG+COBI

		Mean Change from Baseline			
	Baseline	**Week 2**	**Week 4**	**Week 12**	**Week 24**
CD4+ Cell Count (cells/mm^3)	966 (201.7)[a]	-162	-125	-162	-150
CD4%	40 (5.3)[a]	+0.5%	-0.1%	-0.8%	-1.5%

a. Mean (SD)

Adverse Reactions from Clinical Trial Experience in HIV-1 Uninfected Individuals Taking DESCOVY for HIV-1 PrEP

The safety profile of DESCOVY for HIV-1 PrEP was comparable to that observed in clinical trials of HIV-infected subjects based on a double-blind, randomized, active-controlled trial (DISCOVER) in which a total of 5,387 HIV-1 uninfected adult men and transgender women who have sex with men received DESCOVY

(N=2,694) or TRUVADA (N=2,693) once daily for HIV-1 PrEP *[see Clinical Studies (14.3)]*. Median duration of exposure was 86 and 87 weeks, respectively. The most common adverse reaction in participants who received DESCOVY (incidence greater than or equal to 5%, all grades) was diarrhea (5%). Table 2 provides a list of the most common adverse reactions that occurred in 2% or more of participants in either treatment group. The proportion of participants who discontinued treatment with DESCOVY or TRUVADA due to adverse events, regardless of severity, was 1.3% and 1.8%, respectively.

Table 2 Adverse Reactions (All Grades) Reported in ≥2% in Either Arm in the DISCOVER Trial of HIV-1 Uninfected Participants

	DESCOVY (N=2,694)	TRUVADA (N=2,693)
Diarrhea	5%	6%
Nausea	4%	5%
Headache	2%	2%
Fatigue	2%	3%
Abdominal pain[a]	2%	3%

a. Includes the following terms: abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, and abdominal discomfort

Renal Laboratory Tests

Changes from baseline to Week 48 in renal laboratory data are presented in Table 3. The long-term clinical significance of these renal laboratory changes on adverse reaction frequencies between DESCOVY and TRUVADA is not known.

Table 3 Laboratory Assessments of Renal Function Reported in HIV-1 Uninfected Participants Receiving DESCOVY or TRUVADA in the DISCOVER Trial

	DESCOVY (N=2,694)	TRUVADA (N=2,693)
Serum Creatinine (mg/dL)[a] Change at Week 48	−0.01 (0.107)	0.01 (0.111)
$eGFR_{CG}$ (mL/min)[b] Change at Week 48	1.8 (−7.2, 11.1)	−2.3 (−10.8, 7.2)
Percentage of Participants who Developed UPCR >200 mg/g[c] At Week 48	0.7%	1.5%

$eGFR_{CG}$=estimated Glomerular Filtration Rate by Cockcroft-Gault; UPCR=urine protein/creatinine ratio
a. Mean (SD).
b. Median (Q1, Q3).
c. Based on N who had normal UPCR (≤ 200 mg/g) at baseline.

Bone Mineral Density Effects

In the DISCOVER trial, mean increases from baseline to Week 48 of 0.5% at the lumbar spine (N=159) and 0.2% at the total hip (N=158) were observed in participants receiving DESCOVY, compared to mean decreases of 1.1% at the lumbar spine (N=160) and 1.0% at the total hip (N=158) in participants receiving

TRUVADA. BMD declines of 5% or greater at the lumbar spine and 7% or greater at the total hip were experienced by 4% and 1% of participants, respectively, in both treatment groups at Week 48. The long-term clinical significance of these BMD changes is not known.

Serum Lipids

Changes from baseline to Week 48 in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio are presented in Table 4.

Table 4 Fasting Lipid Values, Mean Change from Baseline, Reported in HIV-1 Uninfected Participants Receiving DESCOVY or TRUVADA in the DISCOVER Trial[a]

	DESCOVY (N=2,694)		TRUVADA (N=2,693)	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change[b]	mg/dL	Change[b]
Total Cholesterol (fasted)	176 [c]	0 [c]	176 [d]	-12 [d]
HDL-Cholesterol (fasted)	51 [c]	-2 [c]	51 [d]	-5 [d]
LDL-Cholesterol (fasted)	103 [e]	0 [e]	103 [f]	-7 [f]
Triglycerides (fasted)	109 [c]	+9 [c]	111 [d]	-1 [d]
Total Cholesterol to HDL ratio	3.7 [c]	0.2 [c]	3.7 [d]	0.1 [d]

a. Excludes subjects who received lipid lowering agents during the treatment period.
b. The baseline and change from baseline are for subjects with both baseline and Week 48 values.
c. N=1,098
d. N=1,124
e. N=1,079
f. N=1,107

6.2 Postmarketing Experience

The following reactions have been identified during postapproval use of products containing TAF. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders
Angioedema, urticaria, and rash

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect One or More Components of DESCOVY

TAF, a component of DESCOVY, is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp and BCRP activity may lead to changes

in TAF absorption (see Table 5). Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of DESCOVY and development of resistance. Coadministration of DESCOVY with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

7.2 Drugs Affecting Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of DESCOVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.4)]*.

7.3 Established and Other Potentially Significant Interactions

Table 5 provides a listing of established or potentially clinically significant drug interactions with recommended steps to prevent or manage the drug interaction (the table is not all inclusive). The drug interactions described are based on studies conducted with either DESCOVY, the components of DESCOVY (emtricitabine and tenofovir alafenamide) as individual agents, or are predicted drug interactions that may occur with DESCOVY. For magnitude of interaction, *see Clinical Pharmacology (12.3)*.

Table 5 Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI)		
tipranavir/ritonavir	↓ TAF	Coadministration with DESCOVY is not recommended.
Other Agents		
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓ TAF	Consider alternative anticonvulsant.
Antimycobacterials: rifabutin rifampin rifapentine	↓ TAF	Coadministration of DESCOVY with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ TAF	Coadministration of DESCOVY with St. John's wort is not recommended.

a. This table is not all inclusive.
b. ↓=Decrease

7.4 Drugs without Clinically Significant Interactions with DESCOVY

Based on drug interaction studies conducted with the components of DESCOVY, no clinically significant drug interactions have been either observed or are expected when DESCOVY is combined with the following antiretroviral agents: atazanavir with ritonavir or cobicistat, darunavir with ritonavir or cobicistat, dolutegravir, efavirenz, ledipasvir, lopinavir/ritonavir, maraviroc, nevirapine, raltegravir, rilpivirine, and sofosbuvir. No clinically significant drug interactions have been either observed or are expected when DESCOVY is combined with the following drugs: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to DESCOVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Available data from the APR show no increase in the risk of overall major birth defects for emtricitabine (FTC) compared with the background rate for major birth

defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). There are insufficient tenofovir alafenamide (TAF) data from the APR to adequately assess the risk of major birth defects. The rate of miscarriage for individual drugs is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15−20%.

In animal studies, no adverse developmental effects were observed when the components of DESCOVY were administered separately during the period of organogenesis at exposures 60 and 108 times (mice and rabbits, respectively) the FTC exposure and at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of DESCOVY *(see Data).* Likewise, no adverse developmental effects were seen when FTC was administered to mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose of DESCOVY. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of DESCOVY.

Data

Human Data

Emtricitabine: Based on prospective reports to the APR through January 2019 of over 4,450 exposures to FTC-containing regimens during pregnancy (including over 3,150 exposed in the first trimester and over 1,300 exposed in the second/third trimester), there was no difference between FTC and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.4% (95% CI: 1.9% to 3.0%) with first trimester exposure to FTC-containing regimens and 2.3% (95% CI: 1.5% to 3.2%) with the second/third trimester exposure to FTC-containing regimens.

Tenofovir Alafenamide: Based on prospective reports to the APR of over 220 exposures to TAF-containing regimens during pregnancy (including over 160 exposed in the first trimester and over 60 exposed in the second/third trimester), there have been 6 birth defects with first trimester exposure to TAF-containing regimens.

Methodologic limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Additionally, published observational studies on emtricitabine and tenofovir exposure in pregnancy have not shown an increased risk for major malformations.

Animal Data

Emtricitabine: FTC was administered orally to pregnant mice (250, 500, or 1000 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) through organogenesis (on

gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with FTC in mice at exposures (area under the curve [AUC]) approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the recommended daily dose. In a pre/postnatal development study with FTC, mice were administered doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended daily dose.

Tenofovir Alafenamide: TAF was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures approximately similar to (rats) and 53 (rabbits) times higher than the exposure in humans at the recommended daily dose of DESCOVY. TAF is rapidly converted to tenofovir; the observed tenofovir exposures in rats and rabbits were 59 (rats) and 93 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to tenofovir disoproxil fumarate (TDF, another prodrug for tenofovir) administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 (and lactation day 20) at tenofovir exposures of approximately 14 (21) times higher than the exposures in humans at the recommended daily dose of DESCOVY.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants, to avoid risking postnatal transmission of HIV-1.

Based on limited data, FTC has been shown to be present in human breast milk; it is not known if TAF is present in human breast milk. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *(see Data)*. It is not known if TAF is present in animal milk.

It is not known if DESCOVY affects milk production or has effects on the breastfed child.

Because of the potential for: 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are taking DESCOVY for the treatment of HIV-1 *(see Data)*.

Data

Animal Data

Tenofovir Alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

Treatment of HIV-1 Infection

The safety and effectiveness of DESCOVY, in combination with other antiretroviral agents, for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg *[see Indication and Usage (1.1) and Dosage and Administration (2.3)]*.

Use of DESCOVY in pediatric patients between the ages of 12 to less than 18 years weighing at least 35 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in antiretroviral treatment-naïve HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 35 kg (N=50; cohort 1). The safety and efficacy of FTC+TAF with EVG+COBI in these pediatric subjects was similar to that of HIV-1 infected adults on this regimen *[see Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Use of DESCOVY in pediatric patients weighing at least 25 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in virologically-suppressed pediatric subjects between the ages of 6 to less than 12 years weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to FTC+TAF with EVG+COBI (N=23; cohort 2). The safety in these subjects through 24 weeks of FTC+TAF with EVG+COBI was similar to that of HIV-1 infected adults on this regimen, with the exception of a decrease in mean change from baseline in CD4+ cell count *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg *[see Dosage and Administration (2.3)]*.

Safety and effectiveness of DESCOVY for treatment of HIV-1 infection in pediatric patients less than 25 kg have not been established.

HIV-1 PrEP

Safety and effectiveness of DESCOVY for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg, excluding individuals at risk from receptive vaginal sex, is supported by data from an adequate and well-controlled trial of DESCOVY for HIV-1 PrEP in adults with additional data from safety and pharmacokinetic studies in previously conducted trials with the individual drug products, FTC and TAF, with EVG+COBI, in HIV-1 infected adults and pediatric subjects *[see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3 and 12.4), and Clinical Studies (14)].*

While using DESCOVY for HIV-1 PrEP, HIV-1 testing should be repeated at least every 3 months, and upon diagnosis of any other STIs. Previous studies in at-risk adolescents indicated waning adherence to a daily oral PrEP regimen once visits were switched from monthly to quarterly visits. Adolescents may therefore benefit from more frequent visits and counseling *[see Warnings and Precautions (5.2)].*

Safety and effectiveness of DESCOVY for HIV-1 PrEP in pediatric patients less than 35 kg have not been established.

8.5 Geriatric Use

In clinical trials of an FTC+TAF-containing regimen for treatment of HIV-1, 80 of the 97 subjects enrolled aged 65 years and over received FTC+TAF and EVG+COBI. No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.

8.6 Renal Impairment

DESCOVY is not recommended in individuals with severe renal impairment (estimated creatinine clearance below 30 mL per minute). No dosage adjustment of DESCOVY is recommended in individuals with estimated creatinine clearance greater than or equal to 30 mL per minute *[see Dosage and Administration (2.5) and Clinical Studies (14.2)].*

8.7 Hepatic Impairment

No dosage adjustment of DESCOVY is recommended in individuals with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DESCOVY has not been studied in individuals with severe hepatic impairment (Child-Pugh Class C) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No data are available on overdose of DESCOVY in patients. If overdose occurs, monitor the individual for evidence of toxicity. Treatment of overdose with DESCOVY consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the individual.

Emtricitabine (FTC): Limited clinical experience is available at doses higher than the recommended dose of FTC in DESCOVY. In one clinical pharmacology study,

single doses of FTC 1200 mg (6 times the FTC dose in DESCOVY) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL per minute and a dialysate flow rate of 600 mL per minute). It is not known whether FTC can be removed by peritoneal dialysis.

Tenofovir Alafenamide (TAF): Limited clinical experience is available at doses higher than the recommended dose of TAF. A single dose of 125 mg TAF (5 times the TAF dose in 200/25 mg DESCOVY) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

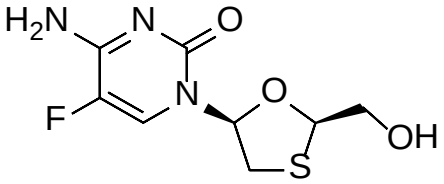
DESCOVY (emtricitabine and tenofovir alafenamide) is a fixed dose combination tablet containing emtricitabine (FTC) and tenofovir alafenamide (TAF) for oral administration.

- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each 200/25 mg tablet contains 200 mg of FTC and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate) and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Emtricitabine: The chemical name of FTC is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-on e. FTC is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

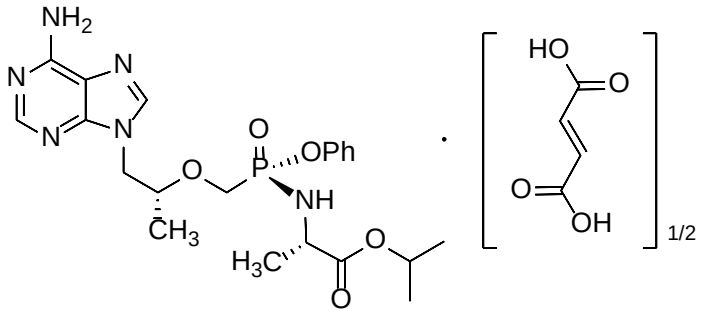
FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24 and has the following structural formula:



FTC is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25 °C.

Tenofovir Alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphin yl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P \bullet ½(C_4H_4O_4)$ and a formula weight of 534.50 and has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DESCOVY is a fixed dose combination of antiretroviral drugs emtricitabine (FTC) and tenofovir alafenamide (TAF) *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT/QTc study in 48 healthy subjects, TAF at the recommended dose or at a dose approximately 5 times the recommended dose, did not affect the QT/QTc interval and did not prolong the PR interval. The effect of the other component of DESCOVY, FTC, or the combination of FTC and TAF on the QT interval is not known.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic (PK) properties of the components of DESCOVY are provided in Table 6. The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir are provided in Table 7. HIV status has no effect on the pharmacokinetics of FTC and TAF in adults.

Table 6 Pharmacokinetic Properties of the Components of DESCOVY

	Emtricitabine	Tenofovir Alafenamide
Absorption		
T_{max} (h)	3	1
Effect of high fat meal (relative to fasting)[a]	AUC Ratio = 0.91 (0.89, 0.93) C_{max} Ratio = 0.74 (0.69, 0.78)	AUC Ratio = 1.75 (1.64, 1.88) C_{max} Ratio= 0.85 (0.75, 0.95)
Distribution		
% Bound to human plasma proteins	<4	~80
Source of protein binding data	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination		
Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
$t_{1/2}$ (h)[c]	10	0.51
% Of dose excreted in urine[d]	70	<1
% Of dose excreted in feces[d]	13.7	31.7

PBMCs=peripheral blood mononuclear cells; CES1=carboxylesterase 1

a. Values refer to geometric mean ratio [High-fat meal/ fasting] in PK parameters and (90% confidence interval). High-calorie/high-fat meal = ~800 kcal, 50% fat.

b. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

c. $t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

d. Dosing in mass balance studies: FTC (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for 10 days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

Table 7 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration with Food in HIV-Infected Adults

Parameter Mean (CV%)	Emtricitabine[a]	Tenofovir Alafenamide[b]	Tenofovir[c]
C_{max} (microgram per mL)	2.1 (20.2)	0.16 (51.1)	0.02 (26.1)
AUC_{tau} (microgram•hour per mL)	11.7 (16.6)	0.21 (71.8)	0.29 (27.4)
C_{trough} (microgram per mL)	0.10 (46.7)	NA	0.01 (28.5)

CV=Coefficient of Variation; NA=Not Applicable

a. From Intensive PK analysis in a phase 2 trial in HIV-infected adults treated with FTC+TAF and EVG+COBI.

b. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC+TAF with EVG+COBI (N=539).

c. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC+TAF with EVG+COBI (N=841).

Specific Populations

Geriatric Patients

Pharmacokinetics of FTC and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of FTC+TAF and EVG+COBI showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

Treatment of HIV-1 Infection: Mean exposures of TAF in 24 pediatric subjects aged 12 to less than 18 years who received FTC+TAF with EVG+COBI were decreased (23% for AUC) and FTC exposures were similar compared to exposures achieved in treatment-naïve adults following administration of this dosage regimen. The TAF exposure differences are not thought to be clinically significant based on exposure-response relationships (Table 8).

Table 8 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide, and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection (N=24).
b. N=23

Exposures of FTC and TAF achieved in 23 pediatric subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (55 lbs) who received FTC+TAF with EVG+COBI were higher (20% to 80% for AUC) than exposures achieved in adults following the administration of this dosage regimen; however, the increase was not considered clinically significant (Table 9) *[see Use in Specific Populations (8.4)]*.

Table 9 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection (N=23).

b. N=22

HIV-1 PrEP: The pharmacokinetic data for FTC and TAF following administration of DESCOVY in HIV-1 uninfected adolescents weighing 35 kg and above are not available. The dosage recommendations of DESCOVY for HIV-1 PrEP in this population are based on known pharmacokinetic information in HIV-infected adolescents taking FTC and TAF for treatment *[see Use in Specific Populations (8.4)].*

Race and Gender

Based on population pharmacokinetic analyses, there are no clinically meaningful differences based on race or gender.

Patients with Renal Impairment

The pharmacokinetics of FTC+TAF combined with EVG+COBI in HIV-infected subjects with renal impairment (eGFR 30 to 69 mL per minute by Cockcroft-Gault method) were evaluated in a subset of virologically-suppressed subjects in an open-label trial (Table 10).

Table 10 Pharmacokinetics of the Components of DESCOVY and a Metabolite of TAF (Tenofovir) in HIV-Infected Adults with Renal Impairment Compared to Subjects with Normal Renal Function[a]

	AUC_{tau} (microgram·hour per mL) Mean (CV%)		
Creatinine Clearance	**≥90 mL per minute (N=18)[b]**	**60–89 mL per minute (N=11)[c]**	**30–59 mL per minute (N=18)**
Emtricitabine	11.4 (11.9)	17.6 (18.2)	23.0 (23.6)
Tenofovir Alafenamide*	0.23 (47.2)	0.24 (45.6)	0.26 (58.8)
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)

*AUC_{last}
a. Trial in HIV-infected adults with renal impairment treated with FTC+TAF with EVG+COBI.
b. From a phase 2 trial in HIV-infected adults with normal renal function treated with FTC+TAF with EVG+COBI.
c. These subjects had an eGFR ranging from 60 to 69 mL per minute.

Patients with Hepatic Impairment

Emtricitabine: The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

Tenofovir Alafenamide: Clinically relevant changes in tenofovir pharmacokinetics in subjects with hepatic impairment were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment *[see Use in Specific Populations (8.7)]*.

Hepatitis B and/or Hepatitis C Virus Infection

The pharmacokinetics of FTC and TAF have not been fully evaluated in subjects infected with hepatitis B and/or C virus.

Drug Interaction Studies

The effects of coadministered drugs on the exposure of TAF are shown in Table 11 and the effects of DESCOVY or its components on the exposure of coadministered drugs are shown in Table 12 [these studies were conducted with DESCOVY or the components of DESCOVY (FTC or TAF) administered alone]. For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 11 Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Drug(s)[a]

Coadministered Drug	Coadministered Drug(s) Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of TAF PK Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 (+100 ritonavir)	10	10	1.77 (1.28, 2.44)	1.91 (1.55, 2.35)	NC
Cobicistat	150	8	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)	NC
Darunavir	800 (+150 cobicistat)	25[b]	11	0.93 (0.72, 1.21)	0.98 (0.80, 1.19)	NC
Darunavir	800 (+100 ritonavir)	10	10	1.42 (0.96, 2.09)	1.06 (0.84, 1.35)	NC
Dolutegravir	50	10	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)	NC
Efavirenz	600	40[b]	11	0.78 (0.58, 1.05)	0.86 (0.72, 1.02)	NC
Lopinavir	800 (+200 ritonavir)	10	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	NC
Rilpivirine	25	25	17	1.01 (0.84, 1.22)	1.01 (0.94, 1.09)	NC
Sertraline	50 (dosed as a single dose)	10[c]	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC

NC=Not Calculated

a. All interaction studies conducted in healthy volunteers.
b. Study conducted with DESCOVY (FTC/TAF).
c. Study conducted with FTC+TAF with EVG+COBI.

Table 12 Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of DESCOVY or the Individual Components[a]

Coadministered Drug	Coadministered Drug Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of Coadministered Drug PK Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 +100 ritonavir	10	10	0.98 (0.89, 1.07)	0.99 (0.96, 1.01)	1.00 (0.96, 1.04)
Darunavir	800 +150 cobicistat	25[b]	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.82, 1.15)
Darunavir	800 +100 ritonavir	10	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 mg	10	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800 +200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam[c]	2.5 (single dose, orally)	25	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NC
	1 (single dose, intravenous)			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25	25	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 (single dose)	10[d]	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC

NC=Not Calculated
a. All interaction studies conducted in healthy volunteers.
b. Study conducted with DESCOVY (FTC/TAF).
c. A sensitive CYP3A4 substrate.
d. Study conducted with FTC+TAF with EVG+COBI.

12.4 Microbiology

Mechanism of Action

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, Ɛ, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide: TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity against HIV-1. Cell culture studies have shown that both tenofovir and FTC can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral Activity in Cell Culture

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary peripheral blood mononuclear cells. The EC_{50} values for FTC were in the range of 0.0013–0.64 micromolar. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 micromolar) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 micromolar).

In a study of FTC with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase strand transfer inhibitors [INSTIs], and PIs) no antagonism was observed for these combinations.

Tenofovir Alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs) no antagonism was observed for these combinations.

Prophylactic Activity in a Nonhuman Primate Model of HIV-1 Transmission

Emtricitabine and Tenofovir Alafenamide: The prophylactic activity of the combination of oral FTC and TAF was evaluated in a controlled study of macaques administered once weekly intra-rectal inoculations of chimeric simian/human immunodeficiency type 1 virus (SHIV) for up to 19 weeks (n=6). All 6 macaques that received FTC and TAF at doses resulting in PBMC exposures consistent with

those achieved in humans administered a dose of FTC/TAF 200/25 mg remained SHIV uninfected.

Resistance

In Cell Culture

Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir Alafenamide: HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

Treatment of HIV-1

The resistance profile of DESCOVY in combination with other antiretroviral agents for the treatment of HIV-1 infection is based on studies of FTC+TAF with EVG+COBI in the treatment of HIV-1 infection. In a pooled analysis of antiretroviral-naïve subjects, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. Genotypic resistance developed in 7 of 14 evaluable subjects. The resistance-associated substitutions that emerged were M184V/I (N=7) and K65R (N=1). Three subjects had virus with emergent R, H, or E at the polymorphic Q207 residue in reverse transcriptase.

One subject was identified with emergent resistance to FTC (M184M/I) out of 4 virologic failure subjects in a clinical study of virologically-suppressed subjects who switched from a regimen containing FTC+TDF to FTC+TAF with EVG+COBI (N=799).

HIV-1 PrEP

In the DISCOVER trial of HIV-1 uninfected men and transgender women who have sex with men and who are at risk of HIV-1 infection receiving DESCOVY or TRUVADA for HIV-1 PrEP, genotyping was performed on participants found to be infected during the trial who had HIV-1 RNA ≥400 copies/mL (6 of 7 participants receiving DESCOVY and 13 of 15 participants receiving TRUVADA). The development of FTC resistance-associated substitutions, M184I and/or M184V, was observed in 4 HIV-1 infected participants in the TRUVADA group who had suspected baseline infections.

Cross-Resistance

Emtricitabine: FTC-resistant viruses with the M184V or I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine-thymidine analog substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution or other substitutions associated with resistance to NNRTIs was susceptible to FTC.

Tenofovir Alafenamide: Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir.

HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine

In long-term carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (23 times the human systemic exposure at the recommended dose of 200 mg per day in DESCOVY) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the recommended dose in DESCOVY).

FTC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

FTC did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times higher exposures (AUC) than in humans given the recommended 200 mg daily dosage in DESCOVY. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended 200 mg daily dosage in DESCOVY.

Tenofovir Alafenamide

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the recommended dose of TDF (300 mg) for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of the daily recommended dose of DESCOVY. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300 mg TDF) and 167 times

(DESCOVY) the exposure observed in humans. In rats, the study was negative for carcinogenic findings.

TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

There were no effects on fertility, mating performance, or early embryonic development when TAF was administered to male rats at a dose equivalent to 62 times (25 mg TAF) the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three- and nine-month administration of TAF; reversibility was seen after a three-month recovery period. No eye toxicity was observed in the dog at systemic exposures of 5 (TAF) and 15 (tenofovir) times the exposure seen in humans with the recommended daily TAF dose in DESCOVY.

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The efficacy and safety of DESCOVY have been evaluated in the trials summarized in Table 13.

Table 13 Trials Conducted with FTC+TAF-Containing Products for HIV-1 Treatment and DESCOVY for HIV-1 PrEP

Trial	Population	Study Arms (N)	Timepoint
Study 104 [a] (NCT01780506) Study 111 [a] (NCT01797445)	HIV-1 infected treatment-naïve adults	FTC+TAF with EVG+COBI [b] (866) FTC+TDF with EVG+COBI [c] (867)	48 Weeks
Study 109 [d] (NCT01815736)	HIV-1 infected virologically suppressed [f] adults	FTC+TAF with EVG+COBI [b] (799) ATRIPLA® or TRUVADA®+atazanavir+cobicistat or ritonavir or FTC+TDF with EVG+COBI [c] (397)	48 Weeks
Study 112 [e] (NCT01818596)	HIV-1 infected virologically suppressed [f] adults with renal impairment [g]	FTC+TAF with EVG+COBI [b] (242)	24 Weeks
Study 106 [e] (Cohort 1) NCT01854775)	HIV-1 infected treatment-naïve adolescents between the ages of 12 to less than 18 years (at least 35 kg)	FTC+TAF with EVG+COBI [b] (50)	48 Weeks
Study 106 [e] (Cohort 2) NCT01854775)	HIV-1 infected, virologically suppressed children between the ages of 6 to less than 12 years (at least 25 kg)	FTC+TAF with EVG+COBI [b] (23)	24 Weeks
DISCOVER [a] (NCT02842086)	HIV-1 uninfected men or transgender women who have sex with men	DESCOVY (2,670) TRUVADA® (2,665)	4,370 person-years[h]

a. Randomized, double-blind, active-controlled study.
b. Administered as GENVOYA®.
c. Administered as STRIBILD®.
d. Randomized, open-label, active controlled trial.
e. Open label trial
f. HIV-1 RNA less than 50 copies per mL.
g. Estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method.
h. Exposure in the DESCOVY group.

14.2 Clinical Trial Results for Treatment of HIV-1

In trials of FTC+TAF with EVG+COBI in HIV-1 infected adults as initial therapy in those with no antiretroviral treatment history (N=866) and to replace a stable antiretroviral regimen in those who were virologically-suppressed for at least 6 months with no known resistance substitutions (N=799), 92% and 96% of patients in the two populations, respectively, had HIV-1 RNA less than 50 copies per mL at Week 48.

An open-label, single arm trial of FTC+TAF with EVG+COBI enrolled 50 treatment-naïve HIV-1 infected adolescents aged 12 to less than 18 years weighing at least 35 kg (cohort 1) and 23 virologically suppressed children aged 6 to less than 12 years weighing at least 25 kg (cohort 2). In cohort 1, the virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) was 92% (46/50) and the mean increase from baseline in CD4+ cell count was 224 cells per mm^3 at Week 48. In cohort 2, 100% of subjects remained virologically suppressed at Week

24. From a mean (SD) baseline CD4+ cell count of 966 (201.7), the mean change from baseline in CD4+ cell count was -150 cells/mm^3 and the mean (SD) change in CD4% was -1.5% (3.7%) at Week 24. All subjects maintained CD4+ cell counts above 400 cells/mm^3 *[see Adverse Reactions (6.1) and Use in Specific Populations (8.4)].*

In a trial in 248 HIV-1 infected adult patients with estimated creatinine clearance greater than 30 mL per minute but less than 70 mL per minute, 95% (235/248) of the combined population of treatment-naïve subjects (N=6) began on FTC+TAF with EVG+COBI and those previously virologically-suppressed on other regimens (N=242) and switched to FTC+TAF with EVG+COBI had HIV-1 RNA less than 50 copies per mL at Week 24.

14.3 Clinical Trial Results for HIV-1 PrEP

The efficacy and safety of DESCOVY to reduce the risk of acquiring HIV-1 infection were evaluated in a randomized, double-blind multinational trial (DISCOVER) in HIV-seronegative men (N=5,262) or transgender women (N=73) who have sex with men and are at risk of HIV-1 infection, comparing once daily DESCOVY (N=2,670) to TRUVADA (FTC/TDF 200 mg/300 mg; N=2,665). Evidence of risk behavior at entry into the trial included at least one of the following: two or more unique condomless anal sex partners in the past 12 weeks or a diagnosis of rectal gonorrhea/chlamydia or syphilis in the past 24 weeks. The median age of participants was 34 years (range, 18-76); 84% were White, 9% Black/Mixed Black, 4% Asian, and 24% Hispanic/Latino. At baseline, 897 participants (17%) reported receiving TRUVADA for PrEP.

At weeks 4, 12, and every 12 weeks thereafter, all participants received local standard of care HIV-1 prevention services, including HIV-1 testing, evaluation of adherence, safety evaluations, risk-reduction counseling, condoms, management of sexually transmitted infections, and assessment of sexual behavior.

Trial participants maintained a high risk of sexual HIV-1 acquisition, with high rates of rectal gonorrhea (DESCOVY, 24%; TRUVADA, 25%), rectal chlamydia (DESCOVY, 30%; TRUVADA, 31%), and syphilis (14% in both treatment groups) during the trial.

The primary outcome was the incidence of documented HIV-1 infection per 100 person-years in participants randomized to DESCOVY and TRUVADA (with a minimum follow-up of 48 weeks and at least 50% of participants having 96 weeks of follow-up). DESCOVY was non-inferior to TRUVADA in reducing the risk of acquiring HIV-1 infection (Table 14). The results were similar across the subgroups of age, race, gender identity, and baseline TRUVADA for PrEP use.

Table 14 HIV-1 Infection Results in DISCOVER Trial – Full Analysis Set

	DESCOVY (N=2,670)	TRUVADA (N=2,665)	Rate Ratio (95% CI)
	4,370 person-years	4,386 person-years	
HIV-1 infections, n	7	15	
Rate of HIV-1 infections per 100 person-years	0.16	0.34	0.468 (0.19, 1.15)

CI = Confidence interval.

Of the 22 participants diagnosed with HIV-1 infection in the trial, five had suspected baseline infection prior to study entry (DESCOVY, 1; TRUVADA, 4). In a case-control substudy of intracellular drug levels and estimated number of daily doses as measured by dried blood spot testing, median intracellular tenofovir diphosphate concentrations were substantially lower in participants infected with HIV-1 at the time of diagnosis compared with uninfected matched control participants. For both DESCOVY and TRUVADA, efficacy was therefore strongly correlated to adherence to daily dosing.

16 HOW SUPPLIED/STORAGE AND HANDLING

DESCOVY 200 mg/25 mg tablets are blue, rectangular-shaped, and film-coated with “GSI” debossed on one side and “225” on the other side. Each bottle contains 30 tablets (NDC 61958-2002-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

- Keep container tightly closed.
- Dispense only in original container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

<u>Important Information for Uninfected Individuals Taking DESCOVY for HIV-1 PrEP</u>

Advise HIV-1 uninfected individuals about the following *[see Warnings and Precautions (5.2)]:*

- The need to confirm that they are HIV-negative before starting to take DESCOVY to reduce the risk of acquiring HIV-1.
- That HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking DESCOVY, because DESCOVY alone does not constitute a complete regimen for HIV-1 treatment.
- The importance of taking DESCOVY on a regular dosing schedule and strict adherence to the recommended dosing schedule to reduce the risk of acquiring HIV-1. Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses.

- That DESCOVY does not prevent other sexually acquired infections and should be used as part of a complete prevention strategy including other prevention measures.
- To use condoms consistently and correctly to lower the chances of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- The importance of knowing their HIV-1 status and the HIV-1 status of their partner(s).
- The importance of virologic suppression in their partner(s) with HIV-1.
- The need to get tested regularly for HIV-1 (at least every 3 months, or more frequently for some individuals such as adolescents) and to ask their partner(s) to get tested as well.
- To report any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.
- That the signs and symptoms of acute infection include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- To get tested for other sexually transmitted infections, such as syphilis, chlamydia, and gonorrhea, that may facilitate HIV-1 transmission.
- To assess their sexual risk behavior and get support to help reduce sexual risk behavior.

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Infection

Inform individuals that severe acute exacerbations of hepatitis B have been reported in patients who are infected with HBV and have discontinued products containing FTC and/or TDF and may likewise occur with discontinuation of DESCOVY *[see Warnings and Precautions (5.1)]*. Advise HBV-infected individuals to not discontinue DESCOVY without first informing their healthcare provider.

Immune Reconstitution Syndrome

Advise HIV-1 infected patients to inform their healthcare provider immediately of any symptoms of infection. In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.3)]*.

New Onset or Worsening Renal Impairment

Advise HIV-1 infected patients and uninfected individuals to avoid taking DESCOVY with concurrent or recent use of nephrotoxic agents. Renal impairment, including cases of acute renal failure, has been reported in association with the use of tenofovir prodrugs *[see Warnings and Precautions (5.4)].*

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to DESCOVY. Advise HIV-1 infected patients and uninfected individuals that they should stop DESCOVY if they

develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Dosage Recommendations for Treatment of HIV-1 Infection

Inform HIV-1 infected patients that it is important to take DESCOVY with other antiretroviral drugs for the treatment of HIV-1 on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2.3)]*.

Pregnancy Registry

Inform individuals using DESCOVY that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to DESCOVY *[see Use in Specific Populations (8.1)].*

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because of the risk of passing the HIV-1 virus to the baby *[see Use in Specific Populations (8.2)]*.

Medication Guide
DESCOVY® (des-KOH-vee)
(emtricitabine and tenofovir alafenamide)
tablets

Read this Medication Guide before you start taking DESCOVY and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

This Medication Guide provides information about two different ways that DESCOVY may be used. See the section **"What is DESCOVY?"** for detailed information about how DESCOVY may be used.

What is the most important information I should know about DESCOVY?

DESCOVY can cause serious side effects, including:

- **Worsening of hepatitis B virus infection (HBV). Your healthcare provider will test you for HBV infection before or when you start treatment with DESCOVY. If you have HBV infection and take DESCOVY, your HBV may get worse (flare-up) if you stop taking DESCOVY. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not run out of DESCOVY. Refill your prescription or talk to your healthcare provider before your DESCOVY is all gone.
  - Do not stop taking DESCOVY without first talking to your healthcare provider.
  - If you stop taking DESCOVY, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection, or give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking DESCOVY.

For more information about side effects, see the section "What are the possible side effects of DESCOVY?"

Other important information for people who take DESCOVY to help reduce their risk of getting human immunodeficiency virus-1 (HIV-1) infection, also called pre-exposure prophylaxis or "PrEP":

Before taking DESCOVY to reduce your risk of getting HIV-1:

- **You must be HIV-1 negative to start DESCOVY. You must get tested to make sure that you do not already have HIV-1 infection.**
- **Do not take DESCOVY for HIV-1 PrEP unless you are confirmed to be HIV-1 negative.**
- Some HIV-1 tests can miss HIV-1 infection in a person who has recently become infected. If you have flu-like symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting DESCOVY or at any time while taking DESCOVY. Symptoms of new HIV-1 infection include:
  - tiredness
  - fever
  - joint or muscle aches
  - headache
  - sore throat
  - vomiting or diarrhea
  - rash
  - night sweats
  - enlarged lymph nodes in the neck or groin

While you are taking DESCOVY for HIV-1 PrEP:

- **DESCOVY does not prevent other sexually transmitted infections (STIs). Practice safer sex by using a latex or polyurethane condom to reduce the risk of getting STIs.**
- **You must stay HIV-1 negative to keep taking DESCOVY for HIV-1 PrEP.**
  - Know your HIV-1 status and the HIV-1 status of your partners.
  - Ask your partners with HIV-1 if they are taking HIV-1 medicines and have an undetectable viral load. An undetectable viral load is when the amount of virus in the blood is too low to be measured in a lab test. To maintain an undetectable viral load, your partners must keep taking HIV-1 medicines every day. Your risk of getting HIV-1 is lower if your partners with HIV-1 are taking effective treatment.
  - Get tested for HIV-1 at least every 3 months or when your healthcare provider tells you.
  - Get tested for other STIs such as syphilis, chlamydia, and gonorrhea. These infections make it easier for HIV-1 to infect you.

- If you think you were exposed to HIV-1, tell your healthcare provider right away. They may want to do more tests to be sure you are still HIV-1 negative.
- Get information and support to help reduce sexual risk behaviors.
- Do not miss any doses of DESCOVY. Missing doses increases your risk of getting HIV-1 infection.

- If you do become HIV-1 positive, you need more medicine than DESCOVY alone to treat HIV-1. DESCOVY by itself is not a complete treatment for HIV-1.

If you have HIV-1 and take only DESCOVY, over time your HIV-1 may become harder to treat.

What is DESCOVY?

DESCOVY is a prescription medicine that may be used in two different ways. DESCOVY is used:

- to treat HIV-1 infection
  - in adults and children who weigh at least 77 pounds (35 kg) together with other HIV-1 medicines
  - in children who weigh at least 55 pounds (25 kg) and less than 77 pounds (35 kg) together with certain other HIV-1 medicines. Your healthcare provider will determine which other HIV-1 medicines may be used with DESCOVY.
- for HIV-1 PrEP to reduce the risk of getting HIV-1 infection in adults and adolescents who weigh at least 77 pounds (35 kg). It is not known if DESCOVY is effective in reducing the risk of getting HIV-1 from certain types of sex.
  - DESCOVY for PrEP is not for use in people born female (assigned female at birth) who are at risk of getting HIV-1 infection from vaginal sex, because its effectiveness has not been studied.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

DESCOVY contains the prescription medicines emtricitabine and tenofovir alafenamide.

It is not known if DESCOVY for treatment of HIV-1 infection is safe and effective in children who weigh less than 55 pounds (25 kg).

It is not known if DESCOVY is safe and effective in reducing the risk of HIV-1 infection in people who weigh less than 77 pounds (35 kg).

For people taking DESCOVY for HIV-1 PrEP:
Do not take DESCOVY for HIV-1 PrEP if:

- **you already have HIV-1 infection.** If you are HIV-1 positive, you need to take other medicines with DESCOVY to treat HIV-1. DESCOVY by itself is not a complete treatment for HIV-1.
- **you do not know your HIV-1 infection status.** You may already be HIV-1 positive. You need to take other HIV-1 medicines with DESCOVY to treat HIV-1 infection.

DESCOVY can only help reduce your risk of getting HIV-1 infection **before** you are infected.

What should I tell my healthcare provider before taking DESCOVY?

Before taking DESCOVY, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including HBV infection
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if DESCOVY can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with DESCOVY.

  Pregnancy Registry: There is a pregnancy registry for people who take DESCOVY during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed.
  - Do not breastfeed if you take DESCOVY for treatment of HIV-1 because of the risk of passing HIV-1 to your baby.
  - One of the ingredients in DESCOVY (emtricitabine) passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines may interact with DESCOVY. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with DESCOVY.
- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take DESCOVY with other medicines.

How should I take DESCOVY?

- Take DESCOVY exactly as your healthcare provider tells you to take it. If you take DESCOVY to treat HIV-1 infection, you need to take DESCOVY with other HIV-1 medicines. Your healthcare provider will tell you what medicines to take and how to take them.
- Take DESCOVY 1 time each day with or without food.
- Do not change your dose or stop taking DESCOVY without first talking with your healthcare provider. Stay under a healthcare provider's care when taking DESCOVY. Do not miss a dose of DESCOVY.
- If you take too much DESCOVY, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your DESCOVY supply starts to run low, get more from your healthcare provider or pharmacy.
  - If you are taking DESCOVY for treatment of HIV-1, the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to DESCOVY and become harder to treat.
  - If you are taking DESCOVY for HIV-1 PrEP, missing doses increases your risk of getting HIV-1 infection.

What are the possible side effects of DESCOVY?

DESCOVY may cause serious side effects, including:

- **See "What is the most important information I should know about DESCOVY?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking medicines to treat HIV-1 infection. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV-1 medicine.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and while taking DESCOVY. Your healthcare provider may tell you to stop taking DESCOVY if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effect of DESCOVY for treatment of HIV-1 is nausea.

The most common side effect of DESCOVY for HIV-1 PrEP is diarrhea.

These are not all the possible side effects of DESCOVY.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DESCOVY?

- Store DESCOVY between 68°F to 77°F (20°C to 25°C).
- Keep DESCOVY in its original container.
- Keep the container tightly closed.

Keep DESCOVY and all medicines out of reach of children.

General information about the safe and effective use of DESCOVY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DESCOVY for a condition for which it was not prescribed. Do not give DESCOVY to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about DESCOVY that is written for health professionals.

What are the ingredients in DESCOVY?

Active ingredients: emtricitabine and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

The tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

208215-GS-3

For more information, call 1-800-445-3235 or go to www.DESCOVY.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 10/2019

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.

/s/

JEFFREY S MURRAY
10/03/2019 01:42:37 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208215Orig1s012

CLINICAL REVIEW(S)

CLINICAL REVIEW AND SUMMARY CDTL

Application Type	Supplemental NDA
Application Number(s)	NDA 208215/S-012
Priority or Standard	Priority
Submit Date(s)	April 5, 2019
Received Date(s)	April 5, 2019
PDUFA Goal Date	October 5, 2019
Division/Office	Division of Antiviral Products/Office of Antimicrobial Products
Reviewer Name(s)	Peter S. Miele, MD – Primary Reviewer Wendy Carter, DO – Cross Discipline Team Leader (CDTL)
Review Completion Date	September 27, 2019
Established/Proper Name	emtricitabine/tenofovir alafenamide (FTC/TAF)
(Proposed) Trade Name	DESCOVY®
Applicant	Gilead Sciences, Inc.
Dosage Form(s)	Fixed-dose combination tablet (emtricitabine 200 mg/tenofovir alafenamide 25 mg)
Applicant Proposed Dosing Regimen(s)	1 tablet once daily
Applicant Proposed Indication(s)/Population(s)	Pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg, excluding those at risk from receptive vaginal sex

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Glossary

Ab	antibody
AE	adverse event
Ag	antigen
AKI	acute kidney injury
ALT	alanine aminotransferase
AMDAC	Antimicrobial Drug Advisory Committee
AR	adverse reaction
AST	aspartate aminotransferase
ATN	Adolescent Medicine Trials Network
B2M	beta-2-microglublin
BIOCF	baseline observation carried forward
BLQ	below level of quantification
BMD	bone mineral density
CASI	computer-assisted self-interview
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHAMPS	Choices for Adolescent Prevention Methods for South Africa
CI	confidence interval
CONRAD	Contraception Research and Development
CRO	contract research organization
CYP3A	cytochrome P4503A
dATP	deoxyadenosine triphosphate
DAVP	Division of Antiviral Products
DBS	dried blood spot
dCTP	deoxycytidine triphosphate
DRISK	Division of Risk Management
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ETASU	Elements To Assure Safe Use
FAS	Full Analysis Set
FDA	Food and Drug Administration
F, FTC	emtricitabine
FTC-TP	emtricitabine triphosphate
GCP	Good Clinical Practice

GHB	gamma hydroxybutyrate
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus-1
HLT	High Level Term
HLGT	High Level Group Term
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IMRS	Interactive Mobile Response System
IND	Investigational New Drug Application
iPrEx	Iniciativa Profilaxis Pre-Exposición
iPSP	Initial Pediatric Study Plan
IWRS	Interactive Web Response System
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LLT	Lower Level Term
LOCF	last observation carried forward
MAED	MedDRA-Based Adverse Event Diagnostics
MedDRA	Medical Dictionary for Regulatory Activities
MG	Medication Guide
MSA	Metropolitan Statistical Area
MSM	men who have sex with men
NAAT	nucleic acid amplification test
NCEP	National Cholesterol Education Program
NDA	New Drug Application
NI	noninferiority
NIH	National Institutes of Health
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
OL	open label
ORA	Office of Regulatory Affairs
ORISE	Oak Ridge Institute for Science and Education
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PADER	Periodic Adverse Drug Experience Report
PBMC	peripheral blood mononuclear cell
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PEP	post-exposure prophylaxis
PeRC	Pediatric Research Committee
PK	pharmacokinetics

PLWH	people living with HIV
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PrEP	pre-exposure prophylaxis
PRT	proximal renal tubulopathy
PSUR	Periodic Safety Update Report
PT	Preferred Term
PY	person-years
PWID	persons who inject drugs
RBP	retinol binding protein
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SD	standard deviation
SHIV	simian/human immunodeficiency type 1 virus
SMQ	Standardized MedDRA Query
sNDA	supplemental New Drug Application
SOC	System Organ Class
STI	sexually-transmitted infection
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TEAE	treatment-emergent adverse event
TGW	transgender women
UIAI	unprotected insertive anal intercourse
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
UPCR	urine protein to creatinine ratio
URAI	unprotected receptive anal intercourse
US	United States
USPI	US prescribing information
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

- Nonproprietary name: emtricitabine (F, FTC)/tenofovir alafenamide fumarate (TAF)
- Proprietary name: Descovy®
- Pharmacologic class: nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs)
- Proposed indication: pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg
- Proposed dosing regimen: one tablet by mouth once daily
- Descovy is currently indicated, in combination with other antiretrovirals, for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg, and in combination with other antiretrovirals other than protease inhibitors that require a cytochrome P4503A (CYP3A) inhibitor in pediatric patients weighing at least 25 kg and less than 35 kg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted efficacy data from a large, active-control trial, Study GS-US-412-2055 (DISCOVER), in 5,335 adult men and transgender women who have sex with men (MSM/TGW) and who are at high risk of HIV-1 infection. Subjects were treated with Descovy (F/TAF 200/25 mg) or the approved PrEP agent Truvada® (emtricitabine/tenofovir disoproxil fumarate, F/TDF 200/300 mg) once daily for a median of 86 and 87 weeks, respectively. The primary endpoint was the incidence of HIV-1 infections per 100 person-years (PY). As of the data cut date for this submission, 22 HIV-1 infections were reported in the trial (F/TAF 7, F/TDF 15) for an HIV-1 incidence rate of 0.160 infections per 100 PY in the F/TAF group and 0.342 infections per 100 PY in the F/TDF group. Despite the low number of infections in the trial, noninferiority of F/TAF to F/TDF was demonstrated based on pre-specified analysis methods. These results provide substantial evidence of F/TAF efficacy to reduce the risk of HIV-1 acquisition from rectal or penile sexual exposure. An efficacy trial in cisgender women was not conducted, and data submitted to support an extrapolation of efficacy based on cervicovaginal drug concentrations were insufficient; thus, evidence of effectiveness in this population is lacking.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

HIV-1 infection is a serious and life-threatening disease affecting approximately 37 million people worldwide. In the United States, an estimated 1.1 million adults and adolescents were living with HIV (diagnosed and undiagnosed) at the end of 2015 {CDC 2019}. There is no cure for HIV-1 infection. Once infection is established, it is a life-long condition that requires chronic therapy with antiretroviral drugs, and if left untreated can lead to AIDS and increased risk of transmission to others.

In 2012, the FDA approved Truvada® (emtricitabine/tenofovir disoproxil fumarate 200/300 mg, F/TDF) for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually-acquired HIV-1 infection in at-risk adults; in 2018, the indication was expanded to include at-risk adolescents weighing at least 35 kg. F/TDF for PrEP is safe and well tolerated and has been shown to decrease the risk HIV-1 acquisition by >95% if taken every day. Currently, about 130,000 persons in the U.S. are using PrEP. Since 2012, the rate of new HIV-1 diagnoses has decreased in the U.S. (possibly due in part to increased PrEP uptake and adherence), but the annual number of new infections has remained stable because the number and rates of diagnoses increased in some subgroups and decreased in others {CDC 2018a}.

While F/TDF is safe and effective, the TDF component has been associated with bone loss and renal toxicity, including proximal renal tubulopathy. Therefore, there remains a need for equally effective but safer drugs for PrEP. In this supplemental application, the Applicant has proposed a PrEP indication for Descovy®, a combination of emtricitabine 200 mg and tenofovir alafenamide fumarate 25 mg (F/TAF), for use in adults and adolescents weighing at least 35 kg. Like TDF, TAF is a prodrug of tenofovir and produces the same active metabolite, tenofovir diphosphate (TFV-DP), in cells. Compared with TDF, however, TAF results in 90% less exposure to tenofovir in plasma and about 4- to 7-fold higher levels of the active TFV-DP in cells. It is hypothesized that the lower plasma levels of tenofovir seen with TAF result in less toxicity to kidneys and bone. On the other hand, TAF has been associated with higher levels of fasting serum cholesterol compared with TDF.

In a large, randomized clinical trial (GS-US-412-2055, DISCOVER), once-daily F/TAF and F/TDF were evaluated for PrEP in over 5,300 adult men and transgender women who have sex with men (MSM/TGW) and who were at high risk of sexually-acquired HIV-1 infection. Subjects in this trial were highly adherent to the daily PrEP dosing regimen, as determined by drug levels in plasma and red blood cells. Importantly, their HIV risk behaviors remained elevated during the trial, as evidenced by self-reporting and high rates of sexually-transmitted infections (STIs). After a median 86-87 weeks of follow-up, only 22 HIV-1 infections were diagnosed in the trial (F/TAF 7, F/TDF 15), which represents a lower HIV-1 incidence rate than previously seen in clinical trials of F/TDF in MSM. Based on these results, FDA concluded that F/TAF and F/TDF are similarly effective in reducing the risk of HIV-1 infection in this population. Claims that suggest F/TAF is superior to F/TDF for PrEP are not supported by

the trial results.

No major safety issues related specifically to F/TAF were identified in this review. F/TAF and F/TDF were both safe and well tolerated, and had similar adverse event profiles, with early gastrointestinal events being the most common adverse reactions reported in both treatment groups. The rates of serious adverse events or adverse events leading to drug discontinuation were low and comparable between the groups. Consistent with previous trials that compared TAF to TDF, the use of F/TAF in this trial resulted in better outcomes at Week 48 with respect to changes from baseline in bone mineral density scans and biomarkers of renal tubular function compared with F/TDF. Whether these subclinical differences can translate to differences in renal or bone adverse events could not be determined in this 96-week trial, as the rates of adverse events or laboratory abnormalities related to renal or bone safety were generally low and comparable between the two groups. Also consistent with prior reports, the use of F/TAF resulted in more subjects having elevated cholesterol levels compared with F/TDF; however, these differences did not result in any major differences related to cardiovascular risk or initiation of lipid modifying agents (it is hypothesized that TDF may have lipid lowering properties related to higher circulating levels of tenofovir in plasma). Compared to F/TDF, use of F/TAF also led to small increases in body weight at 48 weeks (mean increase of 1.1. kg from baseline).

There are no clinical trial data to directly support the use of F/TAF for PrEP in cisgender women or adolescents. An indication in adolescents can be justified by extrapolation of efficacy data from an adult population with comparable HIV-1 sexual risk. In this case, because the dose and pharmacokinetics of F/TAF are the same between adults and adolescents, the adult efficacy data from GS-US-412-2055 can be used to support a PrEP indication in at-risk MSM/TGW adolescents. The safety of F/TAF for PrEP in adolescents is supported by adolescent safety data from HIV-1 treatment trials. Cisgender women, on the other hand, are at risk of HIV-1 acquisition from different routes of sexual exposure (i.e., receptive vaginal sex). An extrapolation approach to support a female indication depends on which pharmacokinetic (PK) compartment is considered most relevant to PrEP efficacy, systemic or local mucosal tissue. As there is no consensus on this matter, adequate PK data in both compartments are needed to support multiple extrapolations of efficacy to cisgender women. Unfortunately, the cervicovaginal tissue PK data submitted with this application were largely uninterpretable. At a meeting of the Antimicrobial Drug Advisory Committee held during this review, most committee members were not convinced that a systemic PK extrapolation approach alone was sufficient to support an indication in this population and recommended that clinical trial data in cisgender women be collected to expand the PrEP indication for F/TAF.

In conclusion, approval of F/TAF for PrEP in at-risk adults and adolescents weighing at least 35 kg, excluding those at risk from receptive vaginal sex, is fully supported by the available evidence of efficacy and safety.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HIV-1 infection affects approximately 37 million people globally and an estimated 1.1 million adults and adolescents in the United States. • There is no cure for HIV-1 infection. Once infection is established, it is a life-long condition that requires chronic therapy with antiretroviral drug regimens to manage. If left untreated, it can lead to Acquired Immunodefiency Syndrome (AIDS), which is associated with significant morbidity and mortality, and increased risk of transmission to others, a major public health concern.	HIV-1 is a serious and life-threatening disease that affects a large population.
Current Treatment Options	• Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, F/TDF) is approved for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 sexual acquisition in at-risk adults and adolescents weighing at least 35 kg. This indication includes both men and women at risk. • The dosing regimen for F/TDF for PrEP is one tablet by mouth once daily. • F/TDF is safe and well tolerated and reduces the risk of HIV-1 infection by more than 95% when used daily. Efficacy is strongly correlated with adherence to the daily dosing PrEP regimen. • Approximately 130,000 persons are currently taking F/TDF for PrEP in the United States. However, the daily oral dosing regimen can be an impediment for some at-risk individuals, such as youth, and can lead to suboptimal adherence or persistence of PrEP use. • The TDF component of F/TDF has been associated with bone loss and renal toxicity, including proximal renal tubulopathy, which occurs in less than 1% of individuals using F/TDF for treatment or prevention.	New drug products that are equally effective but potentially safer and more convenient than currently approved F/TDF are needed for PrEP.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of Descovy® (emtricitabine 200 mg/tenofovir alafenamide 25 mg, F/TAF) for PrEP was established in a randomized, double-blind, active-controlled trial in 5,335 adult men and transgender women who have sex with men (MSM/TGW) and who were at high risk of HIV-1 acquisition from receptive anal sex (GS-US-412-2055, DISCOVER). Subjects were randomized 1:1 to F/TAF or F/TDF, both taken once daily. The primary endpoint was the incidence of HIV-1 infections per 100 person-years (PY) when all subjects had reached 48 weeks of follow-up and 50% had reached 96 weeks. • After median follow-up of 86-87 weeks, 22 HIV-1 infections were observed in the trial (F/TAF 7, F/TDF 15) for an HIV-1 incidence rate of 0.160 infections per 100 PY in the F/TAF group and 0.342 infections per 100 PY in the F/TDF group. The HIV-1 incidence rate ratio of F/TAF to F/TDF was 0.438 (95.003% CI 0.19, 1.15). Because the upper bound of the confidence interval was below the pre-specified noninferiority margin of 1.62, noninferiority of F/TAF to F/TDF was demonstrated. • Efficacy of F/TAF for PrEP was consistent across various subgroups defined by age, race, ethnicity or baseline risk behaviors, although some of these comparisons were limited by subgroup sample size. • A substantial proportion of the trial population demonstrated evidence of insertive penile intercourse; therefore, it is reasonable to apply the F/TAF efficacy results to that risk category as well. • Based on the known similar F/TAF drug exposures between adults and adolescents, and same sexual risk of HIV-1 acquisition, the efficacy of once-daily F/TAF can be extrapolated to support a PrEP indication in at-risk MSM/TGW adolescents.	The submitted clinical data provide substantial evidence of F/TAF efficacy to reduce the risk of HIV-1 acquisition from receptive anal intercourse or insertive penile intercourse in adult MSM/TGW. The data indicate that once-daily F/TAF is noninferior to approved F/TDF; the data do not support claims that F/TAF is superior to F/TDF in terms of efficacy. Based on the same routes of HIV-1 transmission and similar drug exposures between adults and adolescents, the submitted adult efficacy data with F/TAF can be extrapolated to support a PrEP indication in at-risk MSM/TGW adolescents as well. The efficacy of F/TAF for PrEP in adult or adolescent cisgender women, however, has not been evaluated and remains unknown. The labeled indication for F/TAF for PrEP will therefore exclude individuals at risk of HIV-1 acquisition from receptive vaginal sex.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The efficacy of F/TAF for PrEP in adult or adolescent cisgender women is unknown. There are no clinical data to support an F/TAF PrEP indication in this population and the biological differences between men and women in the sites of HIV-1 exposure, and the potential but undefined differences between TAF and TDF in cervicovaginal tissue drug concentrations, preclude extrapolation of efficacy from GS-US-412-2055 in MSM/TGW or from previous trials of F/TDF in women.	The approval of F/TAF for PrEP does not significantly add to the HIV prevention armamentarium, as both F/TAF and F/TDF are similarly effective in reducing the risk of HIV-1, and both share the same once daily dosing regimen. The F/TAF tablet is smaller in size compared FTDF, and this may be considered by some at-risk individuals to be a relevant benefit, thereby potentially improving uptake, adherence and persistence of PrEP use. The lack of a PrEP indication in cisgender women is a serious limitation to the benefit of F/TAF to a U.S. population at risk of HIV-1 infection, where 19% of annual new cases are reported in adult and adolescent women. Clinical trial data in cisgender women are urgently needed to expand the F/TAF PrEP indication to this population. Until then, the availability of a safe and effective product in F/TDF remains a viable PrEP option for these women.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety of F/TAF for PrEP was established in a safety database that included 5,387 individuals in GS-US-412-2055 exposed to F/TAF (n=2694) or F/TDF (n=2693) with a median duration of exposure of 86 and 87 weeks, respectively. • Both F/TAF and F/TDF were safe and well tolerated, with similar adverse event profiles that were generally characterized by mild, self-limited and non-serious events. • The most common adverse drug reactions in both groups were related to gastrointestinal events (nausea, diarrhea, abdominal pain), which tended to occur early after initiation but lead to premature drug discontinuation in less than 1% of subjects. • Where F/TAF demonstrated a potential advantage over F/TDF was in changes from baseline at Week 48 in urinary biomarkers of renal tubulopathy and bone mineral density scans. Whether these subclinical differences can translate to differences in renal or bone adverse events could not be determined in this 96-week trial, as the rates of adverse events or laboratory abnormalities related to renal and bone safety were generally low and comparable between the two groups. The clinical significance of these differences is unclear. • Consistent with previous reports, use of F/TAF was associated with higher levels of fasting serum cholesterol compared with F/TDF. These differences did result in differences in cardiovascular risk. • Use of F/TAF also appeared to result in a mean 1.1 kg increase in body weight at Week 48 compared to no change with F/TDF use. • Drug resistance was observed in 4 subjects in the F/TDF group who were suspected having a baseline HIV-1 infection; all 4 subjects had	No major safety issues related specifically to F/TAF have been identified. F/TAF and F/TDF had similar adverse event profiles in the pivotal trial. F/TAF had less impact on bone mineral density and urinary biomarkers of renal tubular function at Week 48, but the clinical benefit was less apparent. Most of the reported differences were in laboratory tests not done in routine clinical practice, and their clinical significance remains unclear. In the trial, the rates of adverse events or abnormalities on routine laboratory tests related to renal or bone safety were low and comparable between the F/TAF and F/TDF groups. F/TAF was associated with higher levels of fasting serum cholesterol and potential weight gain compared to F/TDF. It is hypothesized that the differences between the two drugs may be due to possible lipid-lowering and weight-suppressive properties of TDF.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	variants expressing the M184VI substitution(s) known to confer resistance to emtricitabine. It is unclear if these variants were transmitted or emerged during F/TDF use. Although no resistance was detected among the 7 subjects in the F/TAF group with HIV-1 infection, the available data are too limited to draw any conclusions regarding the relative risk of resistance between the two drugs.	These issues can be easily monitored and managed in routine clinical practice. All told, the safety differences between F/TAF and F/TDF are not likely to be relevant to the majority of individuals with an indication for PrEP use. For some health care providers, the decision as to which tenofovir-based PrEP regimen to prescribe may depend on whether a given individual has other risk factors related to renal disease, osteoporosis or cardiovascular disease. The landscape for PrEP has changed since F/TDF was first approved in 2012, and both prescribers and PrEP uses are more informed about the safe use of PrEP. Most of the safety concerns associated with F/TAF for PrEP are not new and are adequately addressed in product labeling. Therefore, additional risk mitigation measures are not considered necessary.

1.4. Patient Experience Data

Patient Reported Outcomes: At each visit in the pivotal trial (Study 2055), subjects confidentially completed behavioral assessments via computer-assisted self-interview (CASI) questionnaires.

Clinician Reported Outcomes: In the same trial, clinician reported outcomes were collected to the extent that clinical judgment is required to interpret laboratory and clinical assessments.

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Sec 6.1.2 Study Results
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Sec 8.4 Safety Results
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Human immunodeficiency virus 1 (HIV-1) infection is a life-threatening and serious disease, with 1.7 million people newly infected worldwide in 2018 {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2019}. There is no cure for HIV-1 infection. Once infection is established, it is a life-long condition requiring chronic therapy to manage, which currently consists of daily treatment with antiretroviral (ARV) drugs. If left untreated, HIV-1 infection can lead to Acquired Immunodeficiency Syndrome (AIDS) in the individual, which is associated with significant morbidity and mortality, and increased risk of transmission to others, a major public health concern.

The populations at greatest risk of HIV-1 infection vary by geography, race/ethnicity, social, economic and demographic factors, but mostly include young people, men who have sex with men (MSM), and transgender women (TGW) who have sex with men in the United States (U.S.), North America and Europe, and women and men in areas with high background HIV prevalence. People of color are at particularly high risk {Centers for Disease Control and Prevention (CDC) 2019; UNAIDS 2019}.

In the U.S. and dependent areas, 38,739 people received an HIV-1 diagnosis in 2017 {CDC 2018a}. While the annual rate of HIV-1 diagnoses in the U.S. decreased between 2012 and 2016, the annual number of diagnoses remained stable; the numbers and rates of diagnoses increased in some subgroups and decreased in others. MSM are the population most affected by HIV and accounted for 66% (25,748) of all new HIV-1 diagnoses in 2017, with Black/African American MSM accounting for the largest number of diagnoses (9,807), followed by Hispanics/Latinos (7,436) and whites (6,982).

Adult and adolescent women made up 19% (7,401) of new HIV diagnoses in the U.S. in 2017 {CDC 2018a}, and globally make up 50% of the approximately 37.9 million people living with HIV/AIDS {UNAIDS 2019}. Despite advances in treatment and prevention, HIV/AIDS remains one of the leading causes of death among girls worldwide, and in Africa is one of the leading causes of death in women up to 60 years of age {World Health Organization (WHO) 2019}.

Adolescents are also disproportionately represented among the newly HIV-infected population. Youth aged 13 to 24 years made up 21% (8,164) of new HIV diagnoses in the U.S. and dependent areas in 2017; among these, 21% (1,723) were aged 15 to 19 years {CDC 2018a}.

HIV-1 is mainly spread by having unprotected sex or sharing syringes and other injection equipment with someone who is HIV-infected. Substance use can contribute to these risks

indirectly because alcohol and other drugs can lower people's inhibition and make them less likely to use condoms.

2.2. Analysis of Current Treatment Options

During the majority of the HIV-1 epidemic, condoms and abstinence have been the mainstays of HIV prevention. On July 16, 2012, the U.S. Food and Drug Administration (FDA) approved the fixed-dose combination of FTC 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg (Truvada®, F/TDF) for pre-exposure prophylaxis (PrEP), in combination with safer sex practices, to reduce the risk of sexually-acquired HIV-1 infection in at-risk adults. This approval was based on favorable efficacy and safety data from two large randomized, placebo-controlled trials in diverse populations: 1) the Iniciativa Profilaxis Pre-Exposición (iPrEx) trial (NCT00458393) in MSM/TGW {Grant et. al. 2010}, and 2) the Partners PrEP trial (NCT00557245) in heterosexual HIV serodiscordant couples {Baeten et al. 2012}. In these trials F/TDF was found to be safe and well-tolerated in healthy, HIV-uninfected adults and reduced the risk of HIV acquisition by 42% in MSM/TGW and 75% in individuals in stable serodiscordant relationships (84% and 66% in men and women, respectively). In both trials, and numerous studies since, PrEP efficacy was found to be highly correlated with adherence to the daily dosage regimen of F/TDF. Relative to placebo, an HIV risk reduction rate of up to 95% was estimated among individuals with consistently detectable drug levels. Even higher rates of up to 99% HIV-1 risk reduction have been estimated for individuals with perfect adherence to the daily dosage regimen {Anderson et al. 2012a}. Headache, nausea, abdominal pain and weight loss were the main clinical safety findings associated with F/TDF for PrEP use, often presenting as part of a modest, transient "start-up syndrome" that peaked within the first month of drug administration. Use of F/TDF for PrEP was also associated with small, reversible increases in serum creatinine and decreases in estimated creatinine clearance and bone mineral density (BMD) compared with placebo, but these findings infrequently resulted in clinical adverse events or drug discontinuation. On May 15, 2018, the PrEP indication for Truvada was expanded to include at-risk adolescents weighing at least 35 kg based on extrapolation of adult efficacy data and safety and adherence data from the dedicated open-label Adolescent Medicine Trials Network (ATN) 113 trial (NCT01769456) in young MSM 15 to 17 years of age {Hosek et al. 2017}. F/TDF remains the only drug product approved for a PrEP indication.

Despite demonstrated safety and efficacy, awareness and uptake of F/TDF for PrEP in the U.S. were very limited following the initial approval. However, the CDC estimates that between 2014 and 2016, the annual number of PrEP users aged ≥ 16 years increased by 470% in the U.S., from 13,748 to 78,360 persons {Huang et al. 2018}, and that current PrEP awareness and uptake have increased to 90% and 35%, respectively, among high-risk MSM {Finlayson et al. 2019}. Other sources estimate the number of current U.S. PrEP users to be over 130,000 {AVAC 2019}.

Increases in PrEP uptake have occurred mostly in select populations, namely white, urban, educated MSM. Overall uptake of PrEP in the U.S. remains low. The CDC estimates that 1.1 million people in the U.S. have indications for PrEP use {Smith et al. 2018}; however, only about 7% of these were prescribed PrEP in 2016 {Huang et al. 2018}. Further, there are substantial disparities in awareness and uptake among subgroups disproportionally affected by the HIV epidemic; i.e., MSM and cisgender women of color, transgender persons, adolescents and young adults, people who inject drugs (PWID), and those living in rural communities {Powell et al. 2019}. The latter two are particularly relevant given the ongoing U.S. opioid crisis {Rudd et al. 2016}. To illustrate, the CDC notes that among the 1.1 million U.S. adults with indications for PrEP use, 26%, 44% and 25% were white, black, and Hispanic, respectively; yet among PrEP users with available race/ethnicity data, 69%, 11%, and 13% were white, black, and Hispanic {Huang et al. 2018}. An additional concern is that published data indicate high levels of non-persistence of PrEP use in the U.S. over a two-year period {Coy et al. 2019}. These findings, combined with the stable number of annual new HIV-1 diagnoses in the U.S., point to gaps in the nation's PrEP implementation efforts. In response, the U.S. government announced a new initiative in February 2019 to reduce new HIV-1 infections in the U.S. by 75 percent in five years and by 90 percent by 2030 {Fauci et al. 2019}. A key pillar of the initiative's strategy involves the use of PrEP in at-risk individuals.

Factors contributing to disparities in PrEP uptake and persistence include cost, access, and difficulty adhering to a daily dosage regimen or to frequent provider visits {John et al. 2017}. With regards to the latter, new regimens and delivery methods to improve acceptability, adherence and convenience are needed and currently being explored, including on-demand dosing, long-acting formulations that require less frequent dosing (e.g., every few weeks or months), and new delivery methods (injectables, topical microbicides, vaginal rings, implants).

In addition, while F/TDF is effective for HIV prevention, the TDF component has been associated with BMD loss and adverse renal events, including proximal renal tubulopathy, in both clinical trials and real-world use in people taking F/TDF for PrEP, as well as in people living with HIV (PLWH) taking F/TDF for HIV-1 treatment {Arribas et al. 2017; Kasonde et al. 2014; Liu et al. 2011; Martin et al. 2014; Mills et al. 2015; Mulligan et al. 2015; Sax et al. 2015; Solomon et al. 2014; Tang et al. 2018}. The most serious concern is development of significant renal impairment, or proximal renal tubulopathy, which occurs in less than 1% of individuals taking TDF either for HIV-1 treatment {Nelson et al. 2007; Hamzah et al. 2017} or prevention {Drak et al. 2019}. Nonetheless, these bone and renal safety concerns have the potential to deter the individuals at risk of acquiring HIV infection from using F/TDF for PrEP, especially young persons who are still building bone, and those from populations historically at high risk for renal disease, such as African-Americans and persons with comorbidities such as diabetes and hypertension {Cohen et al. 2017; Mallipattu et al. 2014}.

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant ndication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
FDA Approved Treatments						
Truvada® (F/TDF)	HIV-1 PrEP	2012	Oral, once daily	Two adequate and well-controlled trials in MSM/TGW and heterosexual men and women; HIV risk reduction 42%-84% relative to placebo, but up to 95% with evidence of drug adherence	Safe and well-tolerated. Risk of BMD loss, renal adverse events, and hepatitis B virus (HBV) reactivation in HBV-infected individuals	Approved for use in at-risk adults and adolescents weighing at least 35 kg (indication covers all sexual routes of HIV-1 exposure)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Descovy (F/TAF) was approved in the U.S. on April 4, 2016, for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg, and also in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing 25 kg to 35 kg. By and large, the drug has been safe and well tolerated in postmarketing. An update to the postmarketing section of labeling is included in this application to add the adverse reactions of rash, urticaria, and angioedema based on a Periodic Adverse Drug Experience Report (dated January 21, 2019). Postmarketing pediatric studies, as required under the Pediatric Research Equity Act (PREA), are ongoing in HIV-infected children 4 weeks to 12 years of age.

3.2. Summary of Presubmission/Submission Regulatory Activity

Investigation New Drug (IND) 127728 for F/TAF for a PrEP indication was opened in the U.S. in April 2016; however, preliminary discussions regarding this indication began in February 2016 under IND 111851, the HIV-1 treatment IND for F/TAF.

The originally proposed registrational strategy for PrEP licensure consisted of a single-arm, open-label trial in high-risk MSM/TGW administered once-daily F/TAF for 24 weeks using historical controls for the evaluation of efficacy (i.e., the placebo HIV incidence rates from

previously conducted trials of F/TDF for PrEP in MSM). Integral to this approach was the supposition that intracellular tenofovir diphosphate (TFV-DP) concentrations in peripheral blood mononuclear cells (PBMCs) could serve as a pharmacologic bridge to efficacy data from the F/TDF PrEP trials. However, given reports of lower (i.e., unquantifiable) TFV-DP concentrations in rectal tissue with TAF dosing relative to TDF {Cottrell et al. 2017}, and uncertainty about the relative importance of mucosal tissue drug concentrations to PrEP efficacy, the FDA did not agree that TFV-DP levels in PBMCs could act as a surrogate marker of protection for registrational purposes and instead recommended the Applicant conduct an active-control, non-inferiority trial of F/TAF versus F/TDF for 96 weeks to support licensure.

> *Reviewer comment: The relative contribution of mucosal tissue drug concentrations versus systemic exposure to tenofovir-based PrEP efficacy is unknown. For further discussion of this topic, refer to Section 4.5 of this review.*

With respect to the ensuing Phase 3 trial GS-US-412-2055 in MSM/TGW (NCT02842086), the FDA provided guidance throughout the protocol development. A non-inferiority assessment of the HIV infection rate ratio between the F/TAF and F/TDF arms was deemed an appropriate analysis method for the primary endpoint, with a noninferiority margin of 1.62 based on equal weighting of efficacy data from three previous PrEP trials of F/TDF in MSM, namely the iPrEx, PROUD, and IPERGAY trials {Grant et al. 2010; McCormack et al. 2016; Molina at al. 2015}.

While two adequate and well-controlled trials are generally recommended to provide substantial evidence of efficacy and safety for registration of a new product, the FDA considered that a single trial may be acceptable for this efficacy supplement if adherence in the trial was high and the treatment effect was robust with strong internal consistency. However, the FDA advised that if the investigational plan for the F/TAF PrEP indication was to only include adult MSM/TGW participants, the labeled claim might be limited to the populations studied.

Since the pre-IND phase, the FDA encouraged the Applicant to consider conducting a trial of F/TAF for PrEP in cisgender women at high risk of HIV-1 acquisition. In subsequent discussions, the Applicant reported challenges in identifying a suitable study design or relevant female cohort for study in sub-Saharan Africa, where such a trial would be conducted. The Applicant also expressed concerns that adherence and perception of risk were highly variable among young women 15-25 years of age living in high HIV prevalence areas (a population with high unmet need) and that the majority would not take a daily oral drug for prevention, citing the experience of the FEM-PrEP and VOICE trials, two large trials of F/TDF in cisgender women in sub-Saharan Africa that failed to demonstrate a protective effect due in large part to poor adherence among trial participants {Van Damme et al. 2012; Marrazzo et al. 2015}. Because F/TDF efficacy results in cisgender women have not been consistent, identifying a noninferiority margin has not been possible, making noninferiority PrEP trials in cisgender women infeasible. In subsequent communications, the Applicant indicated that it planned to pursue an

extrapolation strategy via pharmacokinetic (PK) bridging to support a PrEP indication for F/TAF in cisgender women.

(b) (4)

At a Type B meeting in November 2018 to discuss the contents of the present application, the Applicant described its strategy to support a broad indication for F/TAF for PrEP in at-risk adults and adolescents weighing at least 35 kg. Safety and efficacy data from the pivotal Study GS-US-412-2055 (Study 2055) would support an indication in MSM/TGW. An indication in cisgender women would be supported by 1) extrapolation of F/TAF clinical efficacy from Study 2055 via comparable systemic drug exposures and 2) extrapolation of F/TDF clinical efficacy in cisgender women from the Partners PrEP trial via comparable or higher drug exposures in cervicovaginal tissue. For the latter, the Applicant planned to submit results from (b) (4) in healthy female volunteers conducted (b) (4) by the Contraception Research and Development [CONRAD] organization). Extrapolation of safety in HIV-infected men and women from the TAF development program would provide additional support. Finally, an adolescent indication would be supported by extrapolation of adult PrEP efficacy data and PK and safety data in HIV-infected adolescents treated with TAF-based regimens.

The current supplemental New Drug Application (sNDA) was submitted on April 5, 2019. A priority review was granted because the Applicant used a Rare Pediatric Disease Priority Review Voucher for the application.

3.3. Foreign Regulatory Actions and Marketing History

F/TAF is not approved for a PrEP indication in any country.

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

4.1. Office of Scientific Investigations (OSI)

An Office of Scientific Investigations (OSI) audit was requested of three clinical sites from Study 2055 (Sites 698, 407, and 12936). These sites were selected for inspection because they were among the highest enrollers of subjects, and thus contributed significantly to the overall evaluation of efficacy. On-site inspections found no significant deficiencies or anomalies at any of the audited sites related to data integrity or human subject protection. The OSI concluded that the data from Study 2055 submitted in support of this application appeared reliable based on the available information.

4.2. Product Quality

Descovy is an approved drug product. The F/TAF product used in the pivotal Study 2055 is the same as the currently marketed product.

4.3. Clinical Microbiology

Please refer to the Virology review by Dr. Damon Deming for full details.

Clinical Virology

In Study 2055, the detection of drug-resistant viruses among subjects who became HIV-infected during the trial was limited to variants expressing M184I and/or M184V in the viral reverse transcriptase, substitutions known to confer resistance to FTC. The resistant viruses were detected in 4 subjects in the F/TDF group who were suspected of being acutely infected at the time they began PrEP. It is unclear whether the resistant viruses were transmitted or selected during exposure to drug. These results are consistent with those of earlier PrEP trials of F/TDF (e.g., iPrEx and Partners PrEP), where approximately 50% of subjects who were seronegative but HIV-1 infected at baseline when beginning PrEP harbored M184I/V-expressing variants by the time of seroconversion, but no subjects who seroconverted later in the trial developed resistant variants, presumably due to poor adherence and lack of selective pressure.

Nonclinical Virology

The CDC has developed two nonhuman primate challenge models in macaques relevant to a PrEP indication; i.e., a rectal challenge and a vaginal challenge model.

Rectal Challenge Studies

The Applicant provided a nonclinical study report (PC-412-2001) for a CDC study of F/TAF in rhesus macaques intrarectally challenged with a chimeric simian/human immunodeficiency type 1 virus (SHIV) once weekly {Massud et al. 2016}; the study design was similar to a previously conducted CDC study of F/TDF in the same animal model {Garcia-Lerma et al. 2010}. In the F/TAF study, FTC doses of 20 mg/kg and TAF doses of 1.5 mg/kg were selected based on systemic exposures in animals that were consistent with human PK profiles. Twelve macaques (6 F/TAF, 6 placebo) were intrarectally challenged once weekly with SHIV for up to 19 weeks; each challenge took place 24 hours after the animals received test drug by oral gavage, followed by a second dose administered 2 hours after each challenge. None (0/6) of the animals that received F/TAF became infected with SHIV, while all (6/6) animals given placebo became infected. These results were similar to those of the previously conducted F/TDF study.

A previous study in the same macaque model {Garcia-Lerma et al. 2011}, however, failed to demonstrate the prophylactic activity of TAF monotherapy when dosed at 13.7 mg/kg three days before rectal challenge. In this study, 4/6 animals that received TAF became infected by the 5th challenge, despite high mucosal and systemic tenofovir (TFV) levels and TFV-DP concentration in PBMCs that were 50-fold higher than those seen with TDF. The investigators hypothesized that the lack of prophylactic activity was due to high intracellular levels of deoxyadenosine triphosphate (dATP) that compete with TFV-DP for incorporation into nascent HIV-1 transcripts in rectal lymphocytes. The Applicant notes that the drug regimen in this study lacked FTC and that the dosing regimen was different than the one used in the earlier F/TDF study (i.e., dosing 3 days prior to challenge versus 22 hours before and 2 hours after challenge).

Vaginal Challenge Studies

In a recent CDC study {Massud et al. 2019}, 12 healthy pigtail macaques (6 F/TAF, 6 placebo) were vaginally challenged once-weekly with SHIV; each challenge took place 24 hours after the animal received F/TAF or placebo (saline solution) by oral gavage, followed by a second dose administered 2 hours after each challenge. Animals were challenged for up to 15 weeks. Five (5/6) of the animals that received F/TAF remained uninfected, while all (6/6) of the animals given placebo became infected with SHIV. These results were similar to those of a previous vaginal-challenge study conducted with F/TDF {Radzio et al. 2012}, where none (0/6) of the animals given F/TDF became infected after up to 18 challenges and 6/6 placebo animals became infected with SHIV. Interestingly, the one animal that became infected in the F/TAF group had unexpectedly low levels of TFV-DP in PBMCs at most timepoints, suggesting problems with drug administration in the animal.

The prophylactic activity of TAF monotherapy, when dosed at 1.5 mg/kg 24 hours before and 2 hours after vaginal challenge, was also studied {Massud et al. 2019}. In this study, only 4/9

animals dosed with TAF remained uninfected. Although 2/5 of the infected animals had low TFV-DP concentrations in PBMCs, the remaining 3 had intracellular concentrations comparable to those seen in the uninfected animals. These results were consistent with the rectal challenge study that also indicated limited protection with TAF monotherapy.

> *Reviewer comment: The CDC macaque studies demonstrated that the combination of orally administered F/TAF is effective in preventing SHIV infection following multiple rectal or vaginal challenges. However, TAF monotherapy was found to be less protective in both models, despite seemingly high intracellular TFV-DP concentrations in PBMCs in some of the infected animals. The latter raises concerns about the reliability of PBMC intracellular drug concentrations as surrogates of protection. It is also important to keep in mind that there are potentially substantive differences between these macaque models and the human experience, including differences in drug exposure and the use of surrogate viruses, that may limit the predictive value of these models for human PrEP efficacy.*

4.4. Nonclinical Pharmacology/Toxicology

No new information was submitted.

4.5. Clinical Pharmacology

As noted in Section 3.2, this application contains safety and efficacy data from a pivotal Phase 3 trial conducted in MSM/TGW (Study 2055). The Applicant did not conduct an efficacy trial in cisgender women, proposing instead to extrapolate efficacy data from other clinical trials of PrEP via PK bridging to support an indication in that population. The key clinical pharmacology review question therefore is whether the available data are supportive of such an approach. This section will focus on comparison of TAF and TDF PK in various compartments and the implications to an extrapolation strategy.

Background

Comparison of F/TAF and F/TDF Pharmacokinetics Relevant to an HIV-1 PrEP Indication

As both Descovy and Truvada contain FTC 200 mg, and plasma, intracellular and tissue concentrations of FTC and its active metabolite, emtricitabine triphosphate (FTC-TP), are the same following administration of either product, this discussion will focus on PK differences between TAF and TDF as they relate to the safety and efficacy of F/TAF for PrEP.

> *Reviewer comment: The exact contribution of FTC to PrEP efficacy, and whether this differs by site of HIV-1 exposure (e.g., rectal vs. vaginal), is largely unknown. However, several considerations support the inclusion of FTC in a PrEP regimen: 1) PK studies suggest that FTC-TP accumulates more quickly in mucosal tissues, with better vaginal*

> *tissue concentrations, than TFV-DP {Patterson et al. 2011}; 2) studies in macaques suggest better protection against SHIV infection with the combination of FTC and tenofovir over tenofovir monotherapy in rectal and vaginal challenge models (see Section 4.3); and 3) the combination of two N(t)RTIs is expected to increase the barrier to genetic resistance*.

Both TAF and TDF are prodrugs of tenofovir (TFV) and yield the same active metabolite intracellularly, TFV-DP. The two prodrugs, however, exhibit distinct PK properties. TDF is rapidly converted to TFV by gut and serum carboxylesterases. Consequently, after the administration of TDF, it is almost exclusively tenofovir that circulates in plasma. In contrast, TAF is absorbed intact through the gut, circulates as TAF, and is taken up by peripheral cells, where it is phosphorylated to TFV-DP. Administration of TAF 25 mg, therefore, results in 4- to 7-fold higher intracellular levels of TFV-DP in PBMCs and approximately 90% lower TFV concentrations in plasma compared with administration of TDF 300 mg. This marked reduction in circulating TFV levels is believed to be responsible for the improved measures of bone and renal safety that have been observed with TAF relative to TDF in treatment trials of HIV-1 and chronic hepatitis B virus (HBV) infection. Conversely, fasting plasma lipid levels tend to be higher with TAF than TDF because TDF administration results in higher systemic exposure of TFV, which is hypothesized to have lipid-lowering effects {Cid-Silva et al. 2019}.

The PK differences between TAF and TDF also appear to extend to differences in observable TFV-DP concentrations in the mucosal tissues relevant to HIV-1 acquisition. In a single-dose PK study of TAF in healthy women, investigators found that TFV-DP concentrations were unquantifiable in 87.5% and 75% of cervicovaginal and rectal tissue samples, respectively, following dosing with TAF 25 mg, and could not be quantified in any samples collected after 72 hours {Cottrell et al. 2017}. These findings contrasted to earlier results published from a similarly designed single-dose PK study of TDF conducted by the same investigators {Cottrell et al. 2016}. In comparing these data, TFV-DP exposures in rectal tissue following a single 25 mg dose of TAF were found to be more than 10-fold lower compared with those seen after single-dose administration of TDF 300 mg. Furthermore, TFV-DP concentrations were unquantifiable in 75% more rectal tissue samples and in 35% more female genital tract tissue samples with TAF compared to TDF dosing. Given that 91% of the tissue samples were unquantifiable, results from this single-dose TAF study were inconclusive, but they highlighted the limited understanding of TAF pharmacology at the mucosal tissue level and raised questions about the role of TAF in HIV prevention.

The Role of Mucosal Tissue Drug Exposure and HIV-1 PrEP Efficacy

The relevant site of drug action to prevent HIV-1 infection, or the relative contribution of tissue versus systemic drug concentrations to PrEP efficacy, has not been established. While vaginal and rectal mucosal tissues play a critical role in HIV-1 acquisition, the relative importance of

drug concentrations in these tissues to the prevention of viral entry, integration, local expansion and dissemination is not clear. Given how rapidly HIV-1 disseminates to local and distant lymph nodes, and then to distal organs {Haase 2011}, some may speculate that local tissue drug exposures alone cannot provide complete protection. However, evidence from placebo-controlled clinical trials of topical vaginal microbicides, such as the tenofovir 1% vaginal gel {Abdool Karim et al. 2010} and the dapivirine vaginal ring {Baeten et al. 2016; Nel et al. 2016}, indicate that high local tissue drug concentrations, in the absence of significant systemic drug levels, can reduce the risk of HIV-1 infection from vaginal exposure. In macaque studies, both oral F/TDF and tenofovir vaginal gel were found to be highly protective {Dobard et al. 2012; Garcia-Lerma et al. 2008; Garcia-Lerma et al. 2010; Parikh et al. 2009; Radzio et al. 2012}. It has been further suggested that systemic drug concentrations may act as "back-up" if virus escapes early to lymph nodes, and thus may contribute to PrEP efficacy in this manner {Anderson et al. 2016}.

Efficacy outcomes from various clinical trials of oral PrEP in men and women may also provide insight into the role of mucosal tissue drug concentrations. Multiple trials in MSM, for example, have consistently demonstrated a protective benefit of F/TDF against rectal acquisition of HIV-1, despite suboptimal adherence in early trials and event-driven dosing in more recent trials {Grant et al. 2010; Molina et al. 2015; McCormack et al. 2016}. In contrast, clinical trials of F/TDF in cisgender women have yielded mixed results. Poor adherence has been cited as the reason for PrEP futility in two large trials in African women, the FEM-PrEP and VOICE trials {Van Damme et al. 2012; Marrazzo et al. 2015}, where less than 30% of subjects had PK evidence of recent product use. However, low rates of adherence among MSM/TGW subjects in the iPrEx trial still resulted in a 42% risk reduction compared to placebo, suggesting possible preferential prophylactic activity of F/TDF against rectal HIV-1 exposure {Cottrell et al. 2016; Anderson et al. 2016}. Indeed, studies have shown that TFV-DP concentrations are at least 10-fold higher in rectal tissue compared with vaginal tissue, as measured in tissue homogenates {Patterson et al. 2011; Louissaint et al. 2014; Seifert et al. 2016}, although results obtained with tissue cells (as opposed to homogenates) have shown mixed results, from no difference {Louissaint et al. 2014} to 13-fold higher concentrations in colorectal cells compared to cervicovaginal cells {Seifert et al. 2016}.

This apparent disparity in drug exposure between the female genital tract and rectum would presumably not matter if systemic drug concentrations were the main determinant of PrEP efficacy, as the plasma and intracellular PK profiles of FTC and TFV are comparable between men and women. Taken together, however, these indirect observations suggest that local tissue drug concentrations may play an important role in HIV prevention. Accordingly, the PrEP clinical guidelines published by the CDC include information about the time to achieve maximum TFV-DP concentrations in various compartments (e.g., approximately 7 days for rectal tissue and 20 days for cervicovaginal tissue) {CDC 2018}, and some state guidelines have followed suit in their PrEP prescribing recommendations {New York State Department of Health

2017}.

Additionally, it is not clear what drug concentrations would be considered protective for different mucosal tissues. It has been suggested that TFV-DP tissue concentrations should be corrected for endogenous nucleotides (i.e., dATP) because these compete with TFV-DP for incorporation into the proviral DNA strand to terminate chain elongation. About 5-fold higher dATP levels have been observed in vaginal tissue compared with rectal tissue {Cottrell et al. 2016}, which could suggest that higher TFV-DP concentrations may be required to protect against HIV-1 vaginal exposures.

In conclusion, there is no consensus about the relative contribution of tissue drug concentrations to PrEP activity. Given this, and in the absence of clinical data with F/TAF for PrEP in cisgender women, the FDA considered it important to have comparative TFV-DP concentration data in cervicovaginal tissue following TAF and TDF dosing if bridging of efficacy between F/TDF and F/TAF was to be considered for an approval in cisgender women. Bridging of F/TAF efficacy from men to cisgender women based on systemic PK alone, or based on drug exposure in different mucosal tissues, was not deemed acceptable because protective drug concentrations could differ at the mucosal tissue level and between rectal and vaginal tissues.

Extrapolation of PK Data to Support an HIV-1 PrEP Indication in Cisgender Women

The Applicant proposed two extrapolation approaches to support a PrEP indication in cisgender women. The first was to extrapolate efficacy in MSM/TGW receiving F/TAF in Study 2055 by demonstrating comparable systemic PK (TAF in plasma and TFV-DP in PBMCs) between MSM/TGW and cisgender women. As part of this strategy, the Applicant noted that TAF can quickly (within 2-3 hours after a single dose) achieve intracellular TFV-DP concentrations of 40 fmol/10^6 cells or higher in PBMCs in both men and women, a clinical threshold correlated to a level of adherence associated with > 90% HIV-1 risk reduction (EC_{90}) in prior clinical trials of F/TDF in MSM {Anderson et al. 2012a; Anderson et al. 2012b}. However, while this target concentration might be valid for MSM receiving F/TDF, it may not be applicable to F/TAF given potential differences between TAF and TDF in the correlation between PBMC and mucosal tissue concentrations.

The second approach was to extrapolate efficacy in cisgender women who received F/TDF in the Partners PrEP trial. For this approach, efficacy would be extrapolated by demonstrating comparable or higher TFV-DP concentrations in both PBMCs and cervicovaginal tissue. Since it has already been demonstrated that TFV-DP concentrations in PBMCs are 4-7-fold higher following the administration of TAF relative to TDF, the extrapolation would need to also demonstrate comparable or higher TFV-DP exposures in cervicovaginal tissue following administration of the two drugs. To this end, the Applicant provided data from an external PK study, A15-137 (NCT02904369), conducted by CONRAD ([redacted]).

Study A15-137

Title: *Exploratory Pharmacokinetic and Pharmacodynamic Study of Oral F/TAF for the Prevention of HIV Acquisition*

In October 2018, preliminary results from Study A15-137, a Phase 1 single- and multiple-dose PK study of F/TAF and F/TDF in healthy female volunteers, were presented at a scientific meeting {Schwartz et al. 2018}. The study demonstrated that 14-day administration of F/TAF resulted in a higher percentage of cervicovaginal tissue samples with detectable TFV-DP at 4 hours after the last dose compared with administration of F/TDF. For the purposes of this review, the relevant systemic and tissue PK conclusions from the trial are summarized here; for further details, please refer to the FDA Clinical Pharmacology review by Dr. Jenny Zheng.

Study Design

This was a Phase 1 study in healthy adult female volunteers to evaluate the PK of TAF, TFV, FTC, and their respective intracellular metabolites (TFV-DP and FTC-TP) in PBMCs and mucosal (cervicovaginal and rectal) tissues and fluids following single- and multiple-dose (i.e., once daily for 14 days) administration of F/TAF or F/TDF. The study was conducted at three clinical sites. Treatments were as follows:

- Single-Dose Phase
  - F/TAF 200/25 mg, n=12
  - F/TDF 200/300 mg, n=12
- Multiple-Dose Phase
  - F/TAF 200/10 mg, n=24
  - F/TAF 200/25 mg, n=24
  - F/TDF 200/300 mg, n=24

The following PK samples were collected:

- Plasma for TAF, TFV, and FTC
- PBMC for TFV-DP, FTC-TP, dATP, and deoxycytidine triphosphate (dCTP)
- Rectal and cervicovaginal fluid for TAF, TFV, and FTC
- Rectal, cervical, and vaginal tissue biopsy for TAF, TFV, FTC, TFV-DP, FTC-TP, dATP, and dCTP
  - Rectal tissues: 4 hours post dose following 14-day administration
  - Cervical and vaginal tissues: 4 hours post-dose following single dose administration and 4, 24, and 48 hours following 14-day administration.

Tissue samples were collected in a sparse manner and each subject provided tissue samples at

only one time corresponding to their investigative site; thus, tissue PK parameters for an individual subject or correlations between samples collected at different time points could not be determined.

Study Results

Following single-dose administration of F/TAF or F/TDF, 83% of vaginal tissue samples had TFV-DP concentrations below the limit of quantification (BLQ) at 4 hours post-dose. These findings were consistent with a prior study {Cottrell et al. 2017} where a high percentage (87.5%) of BLQ results were observed in female genital tract tissue following single-dose administration of TAF. In sum, it is not known whether single-dose administration of F/TAF provides higher TFV-DP concentrations in vaginal tissue relative to F/TDF.

Following 14-day administration of F/TAF 200/25 mg, median TFV-DP concentrations in vaginal tissue (151 pmol/g) were 3-fold above the lower limit of quantification (LLOQ) at 4 hours after the last dose. In contrast, 62% (5/8) of vaginal tissue samples in the F/TDF group were BLQ at the same time point (Table 2). Given the limited number of quantifiable samples in the F/TDF group, it was not possible to determine the magnitude of the difference between the two groups with respect to vaginal tissue TFV-DP concentrations. In both groups, TFV-DP concentrations were predominately BLQ at 24 hours and 48 hours after the last dose. Results for cervical tissue samples were largely consistent with those for vaginal tissue.

Table 2: Mucosal Tissue TFV-DP Concentration Following 14-Day Administration of F/TAF 200/25 mg or F/TDF 200/300 mg (Study A15-137)

		Vaginal tissue		Cervical tissue		Rectal tissue	
		F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF
4 hours	% BLQ*	0% (0/8)	62% (5/8)	25% (2/8)	88% (7/8)	31% (9/29)	3% (1/30)
	Median TFV-DP† (pmol/g)	151	N/A	126	N/A	150	2521
24 hours	% BLQ*	80% (12/15)	69% (11/16)	67% (10/15)	81% (13/16)	Not determined	
	Median TFV-DP† (pmol/g)	N/A	N/A	N/A	N/A		
48 hours	% BLQ*	80% (12/15)	79% (11/14)	93% (14/15)	100% (14/14)		
	Median TFV-DP† (pmol/g)	N/A	N/A	N/A	N/A		

* Percentage of samples below the lower limit of quantification (BLQ) = number of samples BLQ/ total number of samples
† Median values of all subjects including those with a value of BLQ
N/A = cannot be determined as the median concentration value was below the lower limit of quantification.
Source: FDA analysis of data from Clinical Study Report Table 15 and Appendix 16.2.5 (individual subject concentration data) from CONRAD Study A15-137

While TFV-DP concentrations were higher in vaginal tissue at 4 hours following 14 days of F/TAF

administration compared to F/TDF, it is unclear whether this finding translates to comparable or higher TFV-DP concentrations at steady-state. For instance, F/TDF may have a delayed C_{max} compared to F/TAF and might achieve higher TFV-DP concentrations in mucosal tissues between 4 hours and 24 hours post-dose.

The systemic PK results from this trial were consistent with previous reports regarding TAF and TDF. Administration of F/TAF 200/25 mg provided 90% lower plasma TFV levels and 4- to 7-fold higher intracellular TFV-DP levels in PBMCs as compared to F/TDF. On the other hand, significantly higher (approximately 17-fold) TFV-DP concentrations in rectal tissue were observed with F/TDF compared with F/TAF at 4 hours post 14-day administration. FTC and FTC-TP concentrations in plasma, PBMCs, and mucosal tissues were comparable between F/TAF and F/TDF, as expected.

Office of Study Integrity and Surveillance

Given the potentially important role of Study A15-137 data to the review of this application, an audit of the analytic portion was requested of the FDA Office of Study Integrity and Surveillance (OSIS). The OSIS and Office of Regulatory Affairs (ORA) inspected the (b) (4) [redacted] where the study samples were analyzed.

While the inspection did not reveal any objectionable conditions, the OSIS concluded that the study data from tissue, PBMCs, cervicovaginal fluid and rectal fluid samples were not acceptable as pivotal data to support a regulatory decision. The OSIS noted that there was considerable variability (CV%) among different tissue samples collected from the same subject at the same time point (possibly due to different biopsy locations, sample density or variation in the collection procedure). In addition, the OSIS considered that the tissue assay may not have adequate sensitivity to support the analysis of TFV-DP in vaginal and cervical tissue samples based on the large percentage of samples that were BLQ.

> *Reviewer comment: Given the study results and OSIS recommendations, tissue PK data from Study A15-137 cannot be used to support an extrapolation approach in cisgender women. As such, the application is left with only a systemic PK extrapolation approach to support an indication in this population. The question of whether such an approach was adequate for an approval was brought before the Antimicrobial Drug Advisory Committee on August 7, 2019, who voted 10 to 8 against approval of F/TAF for PrEP in cisgender women (see Section 9). This application will therefore be approved with a limited indication for use in at-risk adults and adolescents, excluding individuals at risk of vaginal acquisition of HIV-1.*

Study GS-US-412-2055

Clinical pharmacology data obtained in Study 2055 were consistent with the known systemic PK profiles of F/TAF and F/TDF described earlier. In this trial, FTC and TFV in plasma and FTC-TP

and TFV-DP in PBMCs were evaluated at Week 4 (trough concentrations) in a subset (10%) of subjects and for all subjects diagnosed with HIV-1 infection. Mean plasma TFV trough concentrations (C_{tau}) were 84% lower with F/TAF dosing as compared with F/TDF. In PBMCs, the mean TFV-DP C_{tau} was 6.3-fold higher in subjects treated with F/TAF versus F/TDF. The PK parameters for FTC and FTC-TP were similar between the two treatment groups, as expected.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3 lists the clinical trials pertinent to this review, including the one pivotal Phase 3 trial in MSM/TGW that forms the basis of the efficacy and safety review of F/TAF for the proposed indication. A clinical study report and datasets from the external PK trial A15-137 in cisgender women were submitted to (b) (4) (CONRAD) and cross-referenced to this NDA to support a PK extrapolation of efficacy in cisgender women (discussed in Section 4.5).

Table 3: Listing of Clinical Trials

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoint	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
GS-US-412-2055	NCT02842086	Phase 3, randomized, double-blind, multicenter trial; 1:1 randomization	• F/TAF (200 mg/25 mg) once daily by mouth • F/TDF (200 mg/300 mg) once daily by mouth	Incidence of HIV-1 infection per 100 person-years (PY)	96 weeks of blinded study drug followed by optional 48 weeks of open-label F/TAF	F/TAF: 2700 F/TDF: 2699 Total: 5399	HIV-1 negative adult men and TGW aged ≥ 18 years who are at risk of acquiring HIV-1 infection through sexual exposure to men	94 centers 11 countries
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
A15-137	NCT02904369	Phase 1, randomized, open-label multicenter trial in two phases: single dose (SD) and multiple dose (MD) phase	• F/TAF (200 mg/25 mg) once daily by mouth • F/TAF (200 mg/10 mg) once daily by mouth • F/TDF (200 mg/300 mg) once daily by mouth	TAF, TFV, FTC concentrations in plasma after SD and 14 days of daily dosing TFV-DP, FTC-TP, dATP, dCTP concentrations in PBMCs and CV and rectal tissue after SD and 14 days of daily dosing F/TAF systemic PK	SD: 1 day MD: 14 days	*MD only:* F/TAF 200/10: 26 F/TAF 200/25: 24 F/TDF: 25	HIV-1 negative adult cisgender women 18-50 years of age	3 centers 2 countries

CV=cervicovaginal; dATP=deoxyadenosine triphosphate; dCTP=deoxycytidine triphosphate; F, FTC=emtricitabine; FTC-TP=emtricitabine triphosphate; MD=multiple dose; SD=single dose; TAF= tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; TFV-DP=tenofovir diphosphate

5.2. Review Strategy

The clinical trial data from Study GS-US-412-2055 (Study 2055) were used as the basis for the efficacy and safety review of this application. This was an adequate and well-controlled trial conducted in a relevant population at risk of HIV-1 acquisition. This reviewer performed the majority of the safety analyses, with occasional data analysis from Maximillian Rohde, BS, a staff fellow in the CDER Oak Ridge Institute for Science and Education (ORISE) program under direction of Dr. Wendy Carter, Cross Discipline Team Leader (CDTL). The review of efficacy was conducted by the FDA statistical reviewer, Dr. Wen Zeng, and pertinent virology and resistance issues were reviewed by the FDA microbiology reviewer, Dr. Damon Deming. Clinical pharmacology data were reviewed by the FDA clinical pharmacology reviewer, Dr. Jenny Zheng.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study GS-US-412-2055 (DISCOVER)

6.1.1. Study Design

Overview and Objective

Title: *A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are at Risk of HIV-1 Infection.*

The purpose of Study 2055 was to determine whether F/TAF would be equally effective and have improved bone and renal safety compared with F/TDF when used for PrEP in MSM/TGW at risk of acquiring HIV-1 infection. Study 2055 serves as the pivotal trial to support the licensure of F/TAF for PrEP in at-risk individuals.

The primary objective of the trial was as follows:

- To assess the rates of HIV-1 infection in MSM/TGW who are administered daily F/TAF or F/TDF with a minimum follow-up of 48 weeks and at least 50% of participants with 96 weeks of follow-up after randomization

Secondary objectives included:

- To compare bone safety between F/TAF and F/TDF as determined by dual energy x-ray absorptiometry (DXA) tests of hip and spine BMD in a subset of subjects at Week 48 and Week 96 in the blinded phase

- To compare renal safety between F/TAF and F/TDF as determined by urine retinol-binding protein (RBP) to creatinine ratio, urine beta-2-microglobulin (β2M) to creatinine ratio, urine protein to creatinine ratio (UPCR), and serum creatinine at Week 48 and Week 96 in the blinded phase
- To compare the general safety between the two treatments

Exploratory objectives included:

- To evaluate the PK of intracellular TFV-DP and FTC-TP in PBMCs
- To access adherence using TFV-DP in dried blood spot (DBS) along with FTC and/or TFV levels in plasma

Trial Design

Study 2055 is an ongoing randomized, double-blind, active-control, non-inferiority trial to compare the safety and efficacy of F/TAF versus F/TDF administered orally once daily for at least 96 weeks in HIV-1 uninfected adult MSM/TGW at risk of acquiring HIV-1 infection through sexual exposure to men. The primary endpoint is the incidence of HIV-1 infection per 100 person-years (PY) when all subjects had reached 48 weeks and 50% had reached 96 weeks of follow-up. The trial is being conducted in the U.S., Canada, and Europe in cities known to be historic urban epicenters of the HIV epidemic and with high prevalence of PLWH, as well as in cities where new HIV-1 cases are increasing, and HIV-associated sexual risk behavior is high.

> *<u>Reviewer comment</u>: The Applicant points out that since F/TDF was approved for PrEP in 2012, HIV-1 infection rates have steadily declined in many places, in part due to the greater uptake and adherence to PrEP but also due to other public health measures such as treatment as prevention (TasP), linkage to care, and risk reduction education. In the U.S., the HIV-1 infection rate for individuals with an indication for PrEP use was 4.14 and 3.74 new cases per 100 PY in 2012 and 2014, respectively, but declined to 3.38 and 3.26 per 100 PY by 2016 and 2017 (Mera et al. 2019). Per the Applicant, this reduction of the "placebo rate" over time makes site selection and eligibility criteria for new PrEP trials essential to maximize the likelihood of enrolling high-risk subjects. Study 2055 was therefore conducted at sites with high HIV incidence and prevalence, and eligibility criteria were selected to recruit a high-risk population (see below). The CDC reports that while the rate of diagnoses of HIV infection in the U.S. decreased between 2012 and 2016, the annual number of new diagnoses remained stable, including among MSM {CDC 2018a}.*

<u>Dose Selection</u>

The approved dose of F/TAF 200 mg/25 mg was selected for evaluation as PrEP. The 200 mg dose of FTC represents the dose in F/TDF approved for PrEP. The TAF 25 mg dose was shown to

result in near-maximal antiviral activity in a Phase 1 monotherapy trial in HIV-infected adults (Study GS-US-120-0104).

Active Control and Noninferiority Margin

Because F/TDF is standard of care for PrEP, placebo-controlled PrEP trials are unethical in most parts of the world and an active comparator arm with F/TDF must be used. This is the first active-controlled PrEP trial to report results.

For this trial in MSM/TGW, a noninferiority (NI) assessment of the HIV infection rate ratio between the F/TAF and F/TDF treatment groups was deemed appropriate for the primary endpoint analysis, consistent with FDA guidance {2019}.

A noninferiority margin of 1.62 per 100 PY and an HIV-1 infection rate of 1.44 per 100 PY in the F/TDF arm, with a 95% confidence interval (CI) of 2.64 to 9.70, were determined based on equal weighting of efficacy data from three previous PrEP trials of F/TDF in similar MSM/TGW populations, namely the iPrEx, PROUD, and IPERGAY trials (Table 4). The NI margin of 1.62 per 100 PY is the square-root of the lower bound of the 95% CI (2.64) of the pooled HIV infection rate ratio to preserve 50% of treatment effect. Please refer to the FDA biostatistical review by Dr. Zeng for further details regarding the method and adequacy of determining the NI margin.

A sample size of 2500 subjects in each arm with 1:1 randomization was expected to provide at least 82% power to show noninferiority of F/TAF to F/TDF.

Table 4: Efficacy of F/TDF from Previous PrEP Trials in MSM

Clinical Trial	Sample Size Placebo (PY Follow-Up)	Sample Size F/TDF (PY Follow-Up)	HIV Infections (Incidence per 100 PY [95% CI])		Rate Ratios in HIV Infection Rates, per 100 PY [95% CI]	Enrolment
			PBO	F/TDF		
iPrEX (URAI subgroup) at screening	753 (1054)	732 (1055)	56 (5.3) [4.0, 6.8]	23 (2.2) [1.4, 3.2]	2.4 [1.5, 3.9]	July 10, 2007 - Dec 17, 2009
PROUD	255 (222)	268 (243)	20 (9.0) [5.6, 13.4]	3 (1.2) [0.3, 3.5]	7.3 [2.2, 24.2]	Nov 29, 2012 – Apr 30, 2014
IPERGAY	201 (212)	199 (220)	14 (6.6) [3.9, 10.6]	2 (0.9) [0.2, 3.2]	7.3 [1.7, 31.6]	Feb 22, 2012 – Oct 23, 2014
Pool	1209 (1488)	1199 (1518)	90 (6.0) [4.9, 7.5] {6.96}*	28 (1.9) [1.3, 2.6] {1.44}*	5.1* [2.64, 9.70]*	

PBO=placebo; PY=person years; URAI=unprotected receptive anal intercourse
* The pooled incidence rate for placebo and F/TDF, based on equal weighting of the three trials
Source: Statistical Analysis Plan for Study GS-US-412-2055

Eligibility Criteria

Subjects in Study 2055 were HIV-1 negative men or transgender women aged ≥ 18 years who had at least 1 of the following: condomless anal intercourse with at least 2 unique male partners with HIV-1 infection or of unknown HIV status in the past 12 weeks, a documented history of syphilis in the past 24 weeks, or a documented history of rectal gonorrhea or chlamydia in the past 24 weeks. These criteria ensured that subjects were actively engaging in sexual risk behavior that increased their likelihood of HIV-1 acquisition at study entry. These criteria are also consistent with or require higher sexual risk than the criteria employed in the iPrEx, PROUD and IPERGAY clinical trials in MSM/TGW, and require higher sexual risk than the definition of "high risk" found in the CDC PrEP clinical guidelines {CDC 2018b}. Subjects who were currently taking F/TDF for PrEP at screening were eligible to participate.

HIV-1 status at study entry was based on a 4th generation antibody (Ab) test. Each subject had estimated glomerular filtration rate according to the Cockcroft-Gault formula ($eGFR_{CG}$) > 60 mL/min and no history of osteoporosis or bone fragility fractures. Individuals with suspected or known active, serious infection(s); evidence of acute viral hepatitis A, B, or C infection; or evidence of chronic HBV infection were excluded.

Assignment to Treatment and Blinding

Eligible subjects were randomized 1:1 to one of the two following treatment groups:

- F/TAF (+ placebo-to-match F/TDF)
- F/TDF (+ placebo-to-match F/TAF)

Randomization was done by investigators using either the Interactive Web Response System (IWRS) or the Interactive Mobile Response System (IMRS). The IWRS or IMRS assigned study drug bottle numbers of blinded F/TAF plus placebo-to-match F/TDF or blinded F/TDF plus placebo-to-match F/TAF at each study visit for each subject. Study drugs were administered in a blinded fashion.

Administrative Structure

The Applicant and a monitoring contract research organization (CRO) monitored the study sites, including the data recorded in the electronic case report forms (eCRFs), to ensure adherence to the protocol and International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP).

An external multidisciplinary Independent Data Monitoring Committee (IDMC) reviewed the trial's progress and performed interim reviews of the safety data. The IDMC consisted of two

clinicians (including a chair person), a biostatistician, a prevention expert, and a community member. A planned Week 24 IDMC analysis was conducted after approximately the first 50% of enrolled subjects completed their Week 24 visit or prematurely discontinued study drug. Additional IDMC analyses were conducted at Weeks 48 and 72. No formal interim efficacy analysis was planned.

Procedures and Schedule of Assessments

Refer to Appendix 13.1 for the Study 2055 schedule of assessments in tabular form.

Individuals were screened within 30 days of the Day 1 (baseline) visit to determine eligibility. The following procedures were performed at the screening visit:

- Medical history, including self-reported sexual risk events and medications
- Complete physical examination and vital signs
- Genital, rectal, and pharyngeal examination for sexually-transmitted infections (STIs); collection of pharyngeal and rectal swabs and urine for gonorrhea and chlamydia screening by nucleic acid testing
- Rapid HIV-1 antigen/antibody (Ag/Ab) test; if positive, the test was repeated
- Blood sample collection for hematology and chemistry, lipids, and syphilis, virologic testing (HIV-1 Ab by central laboratory and hepatitis B screening), and $eGFR_{CG}$
- Urine sample for dipstick urinalysis and urine proteins
- Computer-assisted self-interview (CASI) for recent sexual risk events and demographics

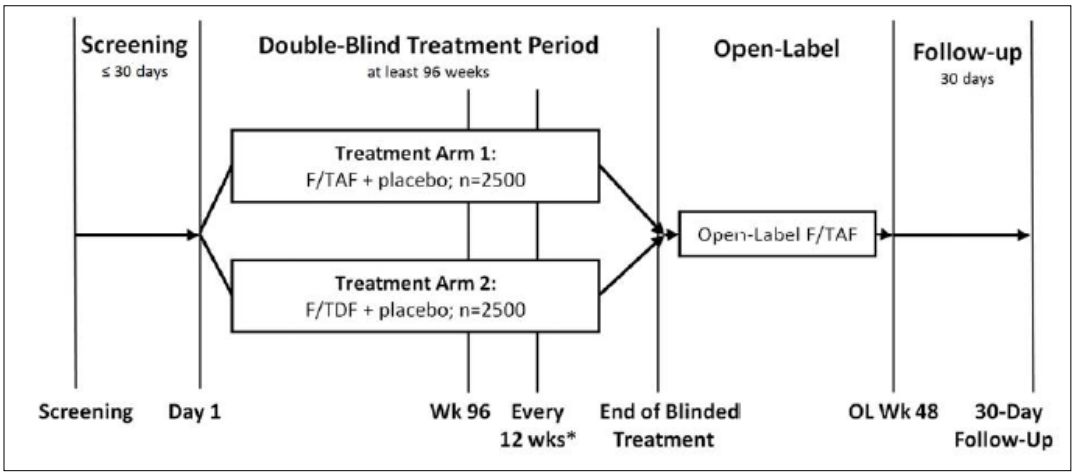
After screening, eligible subjects returned to clinic within 30 days for the Day 1 visit, during which eligibility was confirmed via local tests of 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab. Subjects were then randomized 1:1 to F/TAF or F/TDF and treated for 96 weeks. Subjects were instructed to take study drugs at approximately the same time each day with a full glass of water and without regard to food and to bring all study drugs in the original containers at each clinic visit for drug accountability. Subjects were also instructed about the importance of condom use during the first two weeks of study drug administration.

- At Screening or Day 1, if a subject had a negative rapid test, but had signs or symptoms of acute HIV-1 infection, an HIV-1 RNA by PCR test was completed and if HIV-1 RNA by PCR was positive, the subject was excluded from the trial.

Reviewer comment: The time to maximal protection following PrEP initiation is of vital concern to PrEP users and is a question that has implications for labeling if the approved indication does not include in combination with safer sex practices. At present, there are insufficient data to inform a recommendation. Part of the dilemma is the unknown contribution of mucosal tissue drug concentrations to PrEP efficacy. It is interesting that the Protocol for GS-US-412-2055 recommends use of barrier protection for the first 2 weeks.

Following the Day 1 visit, subjects were required to return for study visits at Weeks 4 and 12, and then every 12 weeks thereafter. Once all subjects reach Week 96, treatment assignments will be unblinded and subjects will be given the option to enter an open-label (OL) phase with open-label F/TAF administered once daily for another 48 weeks (Figure 1).

Figure 1: Study Schema (GS-US-412-2055)



Source: Interim Clinical Study Report for Study GS-412-2055 (Figure 1, page 36)

At each visit, adverse events (AEs) and concomitant medications were assessed. In addition, subjects received adherence and risk reduction counseling, including provision of condoms, and were educated on the signs and symptoms of acute HIV-1 infection.

Blood was collected at Screening, Weeks 4, 12, and then every 12 weeks through the End of Blinded Treatment Phase visit. Laboratory analyses (hematology, chemistry, and urinalysis); STI testing for syphilis (blood), gonorrhea and chlamydia (pharyngeal, rectal, urine); HIV testing (Covance central laboratory tests of HIV-1 Ab/Ag and local tests of 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab); DBS sample collection; and complete or symptom directed physical examinations were performed at all visits. In addition, HIV-1 RNA by PCR test was collected for subjects who (1) had a positive retest rapid HIV-1 Ab/Ag test, (2) had a positive HIV-1 Ab/Ag test, (3) showed symptoms consistent with acute infection regardless of the results of the rapid tests, (4) had a recent exposure that was considered high risk for HIV infection or (5) were confirmed to be HIV infected.

Testing was done for HBV every 24 weeks and hepatitis C virus (HCV) every 48 weeks.

Urine was collected for evaluations of renal function including urine creatinine, urine protein, RBP and β2M at every visit.

Questionnaires assessing HIV risk behavior and adherence were collected at all visits via CASI.

In a subset of approximately 400 subjects at a subset of sites (excluding Germany), DXA scans were performed prior to or within 14 days of the start of study treatment, and then at Weeks 48 and 96, the End of Blinded Treatment Phase visit, OL Week 48, and Early Study Drug Discontinuation Visit, if this occurred > 12 weeks from the prior DXA scan.

Of note, subjects could cease taking study drug either with or without prior notification to the study sponsor. Drug holidays were defined as interruptions for which the subject notified the study sponsor and received pre-approval. Drug interruptions were defined as unapproved gaps in consecutive dosing.

Concomitant and Rescue Medications

Medications listed in Table 5 and the use of herbal/natural supplements were prohibited from use or were to be used with caution while subjects were participating in the trial.

Table 5: Prohibited Medications (GS-US-412-2055)

Medication Class	Medications to be Used with Caution	Prohibited Medications
Antiarrhythmics	Amiodarone and quinidine may increase concentration of TAF and/or TFV.	—
Anticonvulsants	—	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
Antimycobacterials	Clarithromycin may increase concentration of TAF and/or TFV.	Rifapentine, rifabutin, rifampin
Antifungals	Itraconazole, ketoconazole, and voriconazole may increase concentration of TAF and/or TFV.	—
Calcium channel blockers	Diltiazem, felodipine, and verapamil may increase concentration of TAF and/or TFV.	—
Digoxin	Concomitant use may result in an increased or decreased digoxin concentration; use with caution and with appropriate monitoring of serum digoxin concentrations.	—
Herbal/Natural Supplements	—	St. John's wort, Echinacea, Milk thistle (eg, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Hepatitis C therapies	Ledipasvir/sofosbuvir have been shown to increase TFV exposure.	Boceprevir, telaprevir

Nephrotoxic medications	High dose or multiple NSAIDS	Systemic chemotherapeutic agents, aminoglycoside antibiotics, amphotericin B, cidofovir, cisplatin, foscarnet, IV pentamidine, or, other agents with significant nephrotoxic potential
Systemic glucocorticoids	—	Dexamethasone (more than 1 dose), or chronic use of other systemic glucocorticoids
Other	—	Probenecid

Source: Interim Clinical Study Report for Study GS-US-412-2055

Post-exposure prophylaxis (PEP) was permitted for subjects who presented after a high-risk sexual exposure and requested PEP. For these subjects, investigators discontinued study drugs and provided PEP according to local practice or guidelines. Subjects who completed their PEP regimen and wished to continue in the trial were allowed to resume study medication if HIV-1 status was confirmed negative.

Treatment Compliance

Adherence to study drugs was measured via pill counts, responses to adherence questions via CASI, and FTC or TFV levels in plasma.

In addition, DBS samples were collected from all subjects at each post-baseline visit and analyzed for subsets of subjects for TFV-DP and FTC-TP as follows:

- a cohort of approximately 10% of subjects randomly pre-selected to estimate overall rate of adherence in the trial (cohort substudy), and
- all subjects who acquired HIV-1 infection during the trial as well 5 randomly selected matched control subjects who remained uninfected (matched by treatment, time, location, and risk behavior) to assess the association between adherence and efficacy (case-control substudy).

Subject Discontinuation or Withdrawal

Study medication was discontinued for confirmed HIV-1 infection, unacceptable toxicity, or subject request. In addition, study drug could be discontinued for intercurrent illness or subject noncompliance. If a subject discontinued study drug, attempts were made to keep the subject in the trial and continue with the required study-related procedures until the End of Blinded Treatment Phase visit. If this was not possible, the subject could withdraw from the trial.

In general, missing data were not imputed unless methods for handling missing data were specified in the Statistical Analysis Plan (SAP). For example, for the secondary safety endpoints of changes in BMD and urinary biomarkers, missing values were imputed using the last

observation carried forward (LOCF) and baseline observation carried forward (BIOCF) methods

Study Endpoints

The primary endpoint in Study 2055 was the incidence of HIV-1 infection per 100 PY when all subjects had completed 48 weeks of follow-up and at least 50% had completed 96 weeks of follow-up after randomization or were permanently discontinued from the trial. This endpoint was consistent with previous clinical trials of PrEP and FDA guidance {2019}.

- HIV-1 infection was defined by one or more of the following criteria:
    - Serologic evidence (reactive HIV Ab/Ag or Ab test, confirmed by reactive HIV-1/HIV-2 differentiation assay
    - Virologic evidence (positive qualitative HIV-1 RNA or any detectable quantitative HIV-1 RNA test)
    - Evidence of acute HIV-1 infection (reactive p24 Ag or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Ab results)

The Full Analysis Set (FAS) was used for the primary efficacy analysis, and included all subjects randomized into Study 2055 who received at least 1 dose of study drug, were not HIV-positive on Day 1, and had at least one post-baseline HIV laboratory assessment.

A secondary analysis of efficacy is planned when all subjects complete 96 weeks of follow-up.

There were 6 key (α-controlled) secondary safety endpoints, all assessed at Week 48:

- percentage change from baseline in hip BMD
- percentage change from baseline in spine BMD
- percentage change from baseline in urine β2M to creatinine ratio
- percentage change from baseline in urine RBP to creatinine ratio
- distribution of urine protein and UPCR categories
- change from baseline in serum creatinine

Additional endpoints of interest included intracellular TFV-DP and FTC-TP trough concentrations in PBMCs (measured at Week 4), adherence rates using TFV-DP levels in DBS and FTC or TFV levels in plasma, and the frequency of sexual practices associated with increased HIV-1 risk.

Statistical Analysis Plan

The SAP (dated February 20, 2019) was based on study protocol amendment 5, dated September 5, 2018, and was finalized without FDA input before database finalization. The SAP stipulates that the FAS would be used for the primary efficacy analysis and that the Safety Population (consisting of all subjects who received at least 1 dose of study drug) would be used for the analyses of the secondary safety endpoints. All statistical tests were to be 2-sided and

performed at the 5% significance level; however, three interim IDMC analyses prior to the analysis of the primary endpoint were planned with an alpha penalty of 0.00001 for each interim IDMC meeting. Therefore, the alpha level for the primary endpoint was adjusted to 0.04997 (corresponding to 95.003% CI) using the FAS. To control for the overall type I error rate for the multiple safety testings, multiplicity adjustments were performed with a fallback procedure and prespecified 2-sided alpha levels.

The SAP also discusses the planned subgroup analyses for efficacy and safety, the determination of the NI margin, and the methods for handling missing data (the latter two as previously discussed).

> *Reviewer comment: In general, this reviewer concurs with the methods outlined in the SAP. However, among the subgroups prespecified in the SAP for the BMD and renal safety analyses is the subgroup of subjects who were taking F/TDF for PrEP at baseline. While the Applicant reported selected safety results for this subgroup, Study 2055 was not designed as a switch study nor was randomization in the trial stratified by baseline PrEP use. Moreover, safety in this subgroup as reported by the Applicant was not any different than in the overall safety population. Therefore, this reviewer did not include this subgroup in the review of drug-demographic interactions, nor will product labeling include results of the Applicant's subgroup analyses.*

Protocol Amendments

The original protocol was finalized on April 7, 2016 and was amended 5 times (twice before the trial and 3 times during the trial). The most recent protocol version (Amendment 5) was finalized on September 5, 2018. In addition, there were 9 country-specific amendments (4 each in France and Germany, and 1 in the UK). All subjects were enrolled under either Amendment 2 or 3. Important modifications to the protocol included:

- Addition of 3rd generation HIV-1 Ab test for use when the 4th generation rapid HIV-1 Ag/Ab test is unavailable
- Addition of HCV Ab testing to be performed at screening and every 12 months
- Addition of swabs at each visit (except Day 1) to assess gonorrhea and chlamydia
- Addition of HBV serology testing at screening and every 6 month
- Clarified that urinalysis at all visits was to be performed by central laboratory
- Omitted bisphosphonates from the list of prohibited medications to allow for management of osteopenia or osteoporosis
- Removed the requirement to stop prior use of F/TDF for PrEP so as not to eliminate the protective F/TDF benefit prior to study entry
- Addition of an explanation at Day 1 visit about the time to onset of protection upon initiation of study drug and hence the importance of barrier protection during the first 2 weeks of study drug administration

- Updated text for potential high-risk exposure to allow for PEP management
- Provided additional details on members and meeting frequency of the IDMC
- Altered the order of the alpha-controlled secondary safety endpoints to the order currently listed
- Clarified that the evaluation of secondary safety endpoints is not conditioned on the evaluation of primary efficacy endpoint
- Specified that subjects who discontinued study drug prior to the end of the blinded treatment phase visit were ineligible to continue in the OL phase
- Clarified that HIV tests had to be performed in subjects who wished to resume study drug dosing after an interruption of > 14 consecutive days

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that Study 2055 was conducted in accordance with the ICH GCP guidelines and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC, as well as other local legislation.

The protocol, protocol amendments, consent forms, study participant information sheets, administrative letters, and advertisements were submitted by each investigator to a duly constituted independent ethics committee (IEC) or institutional review board (IRB) for review and approval before study initiation. Protocol amendments and all revisions to the consent form or study participant information sheet after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators (see Section 0). Of the 673 investigators that participated in Study 2055, a total of 42 (6%) had disclosable financial interests; for each such investigator, an FDA Form 3455 and the Applicant's Minimization of Bias Form were submitted. The study design of Study 2055 (i.e., a randomized, double-blinded trial with an objective primary endpoint assessed at a central laboratory) minimized potential bias related to these financial interests. No actions were taken or deemed necessary to address this situation.

Patient Disposition

Screening for Study 2055 began in September 2016, and full enrollment was completed in June

2017. A total of 5,857 individuals were screened for eligibility. There were 364 screen failures, including 49 individuals who tested HIV positive at screening. An additional 94 subjects met all eligibility criteria but were not randomized, mostly because they were lost to follow-up or withdrew consent.

A total of 5,399 subjects were randomized (F/TAF 2700, F/TDF 2699). Of these, 12 subjects were randomized but never treated (reasons included: protocol violation 1, withdrew consent 8, HIV-1 infection 2, investigator's discretion 1). The remaining 5,387 subjects constituted the Safety Population (F/TAF 2694, F/TDF 2693). The FAS consisted of 5,335 subjects (F/TAF 2670, F/TDF 2665).

As of the data cut date of January 31, 2019, a total of 4,505 (84%) subjects were still on study drug, whereas 882 (16%) had prematurely discontinued drug. The reasons for premature discontinuation were balanced between the two treatment arms as shown in Table 6.

Table 6: Subject Disposition (GS-US-412-2055)

	Number (%) of Subjects		
	F/TAF	F/TDF	Total
Subjects Screened			5857
Screen Failures			364
HIV Positive at Screening			49
Met Eligibility Criteria but Not Randomized			94
Subjects Randomized	2700	2699	5399
Subjects Randomized but Never Treated	6	6	12
HIV Positive at Baseline	2	0	2
Safety Analysis Set	2694 (100)	2693 (100)	5387 (100)
Full Analysis Set	2670	2665	5335
Subjects Still on Study Drug	2242 (83)	2263 (84)	4505 (84)
Subjects Prematurely Discontinuing Study Drug	452 (17)	430 (16)	882 (16)
Reasons for Prematurely Discontinuing Study Drug			
Death	1 (<1)	2 (<1)	3 (<1)
HIV-1 Infection	4 (<1)	9 (<1)	13 (<1)
Adverse Event	36 (1)	49 (2)	85 (2)
Lost to Follow-Up	201 (8)	170 (6)	371 (7)
Investigator Discretion	5 (<1)	10 (<1)	15 (<1)
Non-Compliance with Study Drug	8 (<1)	12 (<1)	20 (<1)
Protocol Violation	4 (<1)	3 (<1)	7 (<1)
Subject Decision	193 (7)	175 (7)	368 (7)
Subjects Still in Trial	2295 (85)	2328 (86)	4623 (86)
Subjects Prematurely Discontinuing from Trial	399 (15)	365 (14)	764 (14)
Death	1 (<1)	2 (<1)	3 (<1)

HIV-1 Infection	4 (<1)	6 (<1)	10 (<1)
Adverse Event	15 (1)	20 (1)	35 (1)
Lost to Follow-Up	206 (8)	172 (6)	378 (7)
Investigator Discretion	6 (<1)	10 (<1)	16 (<1)
Non-Compliance with Study Drug	6 (<1)	7 (<1)	13 (<1)
Protocol Violation	4 (<1)	2 (<1)	6 (<1)
Withdrew Consent	157 (6)	146 (5)	303 (6)

Source: Adapted from FDA Biostatistical Review (Table 4, page 14) and reviewer's analysis of ADSL dataset

Of note, 22 subjects acquired HIV-1 infection during the trial as of the data cut date. Of these, 13 discontinued study drug at the time of their HIV diagnosis, as mandated by the protocol, but 9 subjects discontinued study drug prior to the HIV-1 diagnosis, reasons included: AE (F/TAF 1, F/TDF 2), noncompliance (F/TDF 2), and subject decision (2 per arm).

Rates of study drug discontinuation were also higher among subjects who were TGW (35%), Black/mixed black (24%), or less than 25 years of age (35%). The reasons for premature drug discontinuation in these subgroups were balanced between treatment arms and were predominately due to loss to follow-up or subject decision.

Protocol Violations/Deviations

A total of 1,435 important protocol deviations were reported in 1,074 subjects; 713 subjects had a single deviation and 361 subjects had 2 or more deviations. Nearly 40% (563/1435) of the deviations were for subjects who missed 1 or more protocol-specified assessments or procedures (e.g., 238 deviations were for central laboratory HIV-1 Ab/Ag not completed). Relevant protocol deviations were proportionally distributed between the treatment groups and study sites (Table 7). None of the important protocol deviations were deemed to have affected the overall quality or interpretation of the study data.

Table 7: Important Protocol Deviations – Full Analysis Set (GS-US-412-2055)

Protocol Deviation Category	DVY (N = 2670)	TVD (N = 2665)
Subjects with at Least 1 Important Protocol Deviation	536 (20.1%)	527 (19.8%)
Missing Data	249	222
Wrong Treatment or Incorrect Dose	124	122
Eligibility Criteria	72	99
Other	67	75
Excluded Concomitant Medication	68	63
Informed Consent	33	41
Off Schedule Procedure	24	18
Total Number of Important Protocol Deviations	710	710
Missing Data	292	263
Wrong Treatment or Incorrect Dose	142	136
Eligibility Criteria	72	101
Other	71	80
Excluded Concomitant Medication	72	69
Informed Consent	34	43
Off Schedule Procedure	27	18

Subjects with multiple protocol deviations were counted only once in each protocol deviation category. For the number of important protocol deviations, subjects with multiple deviations were counted multiple times in each category.
Source: Interim Clinical Study Report for Study GS-US-412-2055

Demographic Characteristics

In Study 2055, the difference between the Safety Population and Full Analysis Set was only 52 subjects and no major differences were noted between the two population sets with respect to demographics or baseline characteristic. Therefore, the demographics and baseline characteristics for the slightly larger Safety Population will be described. Please refer to the FDA biostatistical review for demographics and baseline characteristics of the FAS dataset.

Study 2055 was conducted at 94 sites in 11 countries in North America and Europe, including 55 sites in the United States. All subjects were biologically male at birth. Demographics and baseline characteristics were similar between the two treatment groups, as shown in Table 8. That said, the vast majority (99%) of subjects were MSM; TGW made up only 1% of the study population. Median age was 34 years (range: 18-76 years), with 75% of subjects between 25 and 50 years of age and 12% of subjects < 25 years of age. Most subjects (83%) were white; 9%

were black/mixed black, 4% were Asian, and about 25% were Hispanic or Latino. The majority (60%) of subjects were located in the U.S., of which 40% were located in the U.S. South region. The highest educational level attained by 57% of the study population was 4 years of college or higher; 71% of subjects were employed full-time (data not shown).

> *Reviewer comment: In general, the demographics in Study 2055 skewed towards older, white, educated MSM, reflecting the majority of PrEP users in the U.S.{Smith et al. 2015}. Less represented were subpopulations disproportionally affected by HIV-1, namely trans women, persons of color, and youth. That said, while demographics may play a role in some of the behavioral aspects of PrEP (e.g., uptake, adherence, and persistence), they are not likely to impact efficacy within a biological male population as the routes of HIV transmission and the effect of PrEP to reduce the risk of HIV-1 acquisition, when taken daily, are the same across biological male subpopulations.*

Table 8: Demographics - Safety Analysis Set (GS-US-412-2055)

Demographic Parameters	*Number (%) of Subjects*		
	F/TAF (N=2694)	F/TDF (N=2693)	Total (N=5387)
Sex			
Male	2694 (100)	2693 (100)	5387 (100)
Female	0	0	0
MSM or TGW			
Men Who Have Sex with Men (MSM)	2649 (98)	2664 (99)	5313 (99)
Transgender Women (TGW)	45 (2)	29 (1)	74 (1)
Age			
Mean years (SD)	36 (0.2)	36 (0.2)	36 (0.2)
Median (years)	34	34	34
Min, max (years)	18, 76	18, 72	18, 76
Age Group			
< 18 years	0	0	0
≥ 18 - < 25 years	336 (13)	293 (11)	629 (12)
≥ 25 - < 50 years	2028 (75)	2014 (75)	4042 (75)
≥ 50 - < 65 years	297 (11)	350 (13)	647 (12)
≥ 65 years	33 (1)	36 (1)	69 (1)
Race			
White	2264 (84)	2247 (83)	4511 (84)
Black/Mixed Black	240 (9)	234 (9)	474 (9)
Asian	113 (4)	120 (5)	233 (4)
American Indian or Alaska Native	12 (<1)	14 (<1)	26 (<1)
Native Hawaiian or Other Pacific Islander	17 (1)	23 (1)	40 (1)
Other (Nonblack)	45 (2)	50 (2)	95 (2)
Not Permitted[1]	3	5	8

Ethnicity			
Hispanic or Latino	635 (24)	683 (25)	1318 (25)
Not Hispanic or Latino	2058 (76)	2008 (75)	4066 (76)
Not Permitted[1]	1	2	3
Region			
United States	1591 (59)	1629 (60)	3220 (60)
Rest of the World	1103 (41)	1064 (40)	2167 (40)
Canada	191 (7)	162 (6)	353 (7)
South America	0	0	0
Europe	912 (34)	902 (34)	1814 (34)
Asia	0	0	0
Africa	0	0	0

[1] Data on race and/or ethnicity were not collected because subject refused to answer; excluded from percentage.
Source: Adapted from FDA Biostatistical Review (Table 13, page 24) and reviewer's analysis of ADSL dataset

Other Baseline Characteristics (e.g., HIV risk characteristics)

Study 2055 enrolled an MSM/TGW population at high risk of HIV-1 acquisition, as determined by their baseline risk characteristics. Baseline HIV risk characteristics and medical characteristics relevant to PrEP use were balanced between the treatment groups, as shown in Table 9.

At screening, less than 40% of subjects reported routinely using condoms to manage HIV risk, and less than 30% asked their partners to use condoms. Of those with screening CASI information (n=5199), 61% of subjects reported two or more unique unprotected receptive anal intercourse (URAI) partners in the 90 days prior to screening (mean [SD]: 3.5 [0.1] partners) and 63% reported 2 or more unique unprotected insertive anal intercourse (UIAI) partners (mean [SD]: 4.2 [0.1] partners). In the 24 weeks prior to screening, 10% of subjects reported a history of rectal gonorrhea, 13% a history of rectal chlamydia, and 9% a history of syphilis. At screening, the proportion of subjects diagnosed with STIs, based on laboratory results, was as follows: gonorrhea rectal 4%, urethral 1%, pharyngeal 5%; chlamydia rectal 7%, urethral 2%, pharyngeal 2%; and syphilis 0.2%. In addition, two-thirds of subjects reported recreational drug use in the 3 months prior to screening. Approximately 16% of subjects reported use of PEP in the previous 12 months, and 23% reported any prior use of F/TDF for PrEP. At baseline, 17% of subjects were taking F/TDF for PrEP prior to randomization. Finally, 44% of subjects were uncircumcised.

Table 9: Baseline HIV Risk and Medical Characteristics - Safety Analysis Set (GS-US-412-2055)

Baseline Characteristics	*Number (%) of Subjects*		
	F/TAF (N=2694)	F/TDF (N=2693)	Total (N=5387)
BMI (kg/m^2)			
Mean (SD)	26.3 (0.1)	26.2 (0.1)	26.3 (0.1)
Median	25.3	25.3	25.3
Min, Max	16, 53	17, 62	16, 62

eGFR (mL/min)			
Mean (SD)	127.9 (0.7)	126.4 (0.7)	127.2 (0.5)
Median	122.9	121.2	121.8
Min, Max	60, 345	62, 391	60, 391
Circumcised			
No	1185 (44)	1160 (43)	2345 (44)
History of Rectal Gonorrhea in Past 24 Weeks			
Yes	274 (10)	262 (10)	536 (10)
History of Rectal Chlamydia in Past 24 Weeks			
Yes	342 (13)	333 (12)	675 (13)
History of Syphilis in Past 24 Weeks			
Yes	230 (9)	263 (10)	493 (9)
Baseline Gonorrhea (Positive/Detected)			
Rectal	123 (5)	113 (4)	236 (4)
Urethral	17 (1)	12 (1)	29 (1)
Pharyngeal	103 (5)	130 (6)	233 (5)
Baseline Chlamydia (Positive/Detected)			
Rectal	199 (8)	189 (7)	388 (7)
Urethral	61 (2)	54 (2)	115 (2)
Pharyngeal	47 (2)	43 (2)	90 (2)
Baseline Syphilis			
Yes	7 (<1)	4 (<1)	11 (<1)
URAI Partners in 90 Days Prior to Screening			
Mean (SD)	3.6 (0.1)	3.5 (0.1)	3.5 (0.1)
Median	3	3	3
Min, Max	0, 99	0, 99	0, 99
≤ 2 URAI Partners	1508 (58)	1577 (61)	3085 (59)
> 2 URAI Partners	1094 (42)	1020 (39)	2114 (41)
UIAI Partners in 90 Days Prior to Screening			
Mean (SD)	4.2 (0.1)	4.1 (0.1)	4.2 (0.1)
Median	2	2	2
Min, Max	0, 70	0, 99	0, 99
≤ 2 UIAI Partners	1440 (55)	1476 (57)	2916 (56)
> 2 UIAI Partners	1162 (45)	1121 (43)	2283 (44)
Use Condoms to Manage HIV Risk			
No	1660 (62)	1628 (61)	3288 (61)
Ask Partners to Use Condoms to Manage HIV Risk			
No	1991 (74)	1981 (74)	3972 (74)
Recreational Drug Usage in 3 Months Prior to Screening			
Yes	1785 (67)	1786 (67)	3571 (67)
Any Prior F/TDF for PrEP			
Yes	628 (23)	619 (23)	1247 (23)
Baseline F/TDF for PrEP			
Yes	465 (17)	440 (16)	905 (17)
Number of Times Prescribed PEP for 4 Weeks in Past 12 Months Prior to Screening			
0	2274 (85)	2249 (84)	4523 (84)

1	279 (10)	287 (11)	566 (11)
2	72 (3)	64 (2)	136 (3)
3-5	37 (1)	43 (2)	80 (2)
6-11	6 (<1)	17 (1)	23 (<1)
≥ 12	12 (<1)	17 (1)	29 (1)

BMI=body mass index; eGFR=estimated glomerular filtration rate; PEP=post-exposure prophylaxis; PrEP=pre-exposure prophylaxis; UIAI=unprotected insertive anal intercourse; URAI=unprotected receptive anal intercourse
Source: Adapted from FDA Biostatistical Review (Table 13, page 24) and reviewer's analysis of ADSL dataset

> *Reviewer comment: Based on their baseline HIV risk characteristics, the subjects enrolled into Study 2055 were at high risk of HIV-1 acquisition from URAI. The study population is therefore suitable for an evaluation of PrEP efficacy in MSM/TGW.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

By all measures, estimated adherence to study drugs was high in Study 2055. By CASI questionnaire, the median self-reported adherence was > 95% at all study visits for both treatment groups. Median pill-count adherence was 98% in both groups. In the DBS cohort substudy, the majority of subjects in both groups had TFV-DP levels in red blood cells consistent with high adherence (≥ 4 days of dosing per week). Other objective measures of adherence, such as TFV and FTC levels in plasma and TFV-DP and FTC-TP levels in PBMCs at Week 4, corroborated the high adherence noted in the DBS substudy.

The number of subjects with any PEP use while at risk during the trial was low in both groups: F/TAF 36/2670 (1.3%); F/TDF 37/2665 (1.4%).

Efficacy Results – Primary Endpoint

As of the data cut date, 22 subjects were diagnosed with HIV-1 infection in Study 2055 (F/TAF 7, F/TDF 15), resulting in an HIV-1 infection rate of 0.16 per 100 PY in the F/TAF arm and 0.342 per 100 PY in the F/TDF arm (Table 10). The HIV-1 infection rate ratio of F/TAF versus F/TDF was 0.468 (95.003% CI 0.91, 1.149). Because the upper bound of the 95.003% CI for the rate ratio (i.e., 1.149) was less than the pre-specified NI margin of 1.62, the FDA agreed with the Applicant that Study 2055 demonstrated noninferiority of F/TAF to F/TDF.

Table 10: Primary Efficacy Analysis, HIV Incidence Rates – Full Analysis Set (GS-US-412-2055)

		F/TAF (N=2670)	F/TDF (N=2665)	95.003% CI for Ratio of F/TAF to F/TDF
Person-years of Follow-Up		4369.7	4386.2	
Number of HIV-1 Infection Events		7	15	
HIV-1 Infection Rate per 100 Person-years		0.160	0.342	
Applicant Used	95% Exact CI[a]	0.064, 0.330	0.191, 0.564	
	Rate Ratio	0.438		0.191, 1.149[b]

a) Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
b) 95.003% CI was constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect.
Source: Adapted from FDA Biostatistical Review (Table 6, page 17)

Sensitivity Analyses of the Primary Endpoint

Five of the 22 subjects (F/TAF 1, F/TDF 4) diagnosed with HIV-1 infection during the trial were suspected of having HIV-1 infection at baseline. Four of these subjects were diagnosed within 4 weeks of study entry, and one was diagnosed at 12 weeks; all had potential HIV exposure around the time of study entry. In a sensitivity analysis conducted by FDA statisticians, exclusion of these 5 subjects from the primary efficacy analysis did not change the overall efficacy conclusion. In this analysis, the HIV incidence rate ratio increased from 0.468 to 0.547 (95.003% CI 0.202, 1.481), but the upper bound of the 2-sided 95.003% CI was still below the prespecified NI margin.

In another FDA sensitivity analysis, 15 subjects (F/TAF 9, F/TDF 6) who were excluded from the FAS because they did not have a post-baseline HIV-1 test, but who had received at least 14 days of blinded study drug, were assumed to be HIV-1 infected. Inclusion of these subjects in the primary efficacy analysis increased the total number of HIV-1 infections to 37 (F/TAF 16, F/TDF 21) with a rate ratio of 0.765 (95.003% CI 0.399, 1.466). Again, the upper bound of the 2-sided 95.003% CI was below the prespecified NI margin, thus the overall conclusion did not change.

Lastly, the HIV-1 infection rate observed in the control arm of Study 2055 was 0.342 per 100 PY, which is approximately 4-fold lower than the assumed infection rate of 1.44 per 100 PY based on the historical trials. This finding may raise concerns about the validity of the constancy assumption regarding the treatment effect of F/TDF over placebo. To address this, FDA conducted a sensitivity analysis wherein the NI margin was adjusted to 1.13 (the quadratic root of the original NI margin). Based on this analysis, the upper bound of the 95.003% CI for the rate ratio of F/TAF to F/TDF (i.e., 1.149) exceeds the new NI margin slightly; however, adjustment of the NI margin in a post-hoc manner is a rather conservative approach.

> *Reviewer comment: The most probable explanation for the lower than expected HIV infection rates observed in Study 2055 is that adherence to study drug was much higher than in previous trials, particularly the iPrEx trial. As noted further below, the Applicant provided CDC epidemiological data for the U.S. regions where Study 2055 was conducted and found that as of 2016, when the Study 2055 was initiated, the HIV-1 infection rate was still high at 4.02 per 100 PY (95% CI 3.56, 3.66) among at-risk MSM not using PrEP, thus minimizing concerns that the putative placebo rate had decreased substantially.*

For further details of sensitivity analyses conducted by FDA, please refer to the biostatistical review by Dr. Zeng.

The Applicant also conducted several sensitivity analyses of the primary endpoint. In one such analysis, the Per Protocol (PP) Analysis Set, which excluded subjects with any major protocol violations, was used to evaluate the primary endpoint using the rate ratio method. However, the PP Analysis Set reduced the total number of HIV-1 infections to 7 (F/TAF 2, F/TDF 5) and noninferiority could not be demonstrated.

The Applicant also conducted sensitivity analyses using a risk-difference approach, applying it to both the FAS and PP sets, as well as the FAS excluding subjects with suspected baseline HIV-1 infection, and reported noninferiority of F/TAF to F/TDF in all 3 analyses. FDA statisticians, however, do not consider the risk-difference method appropriate for use in this context due to its instability when the event rate is low, as was the case in Study 2055.

Comparison of Observed HIV Infection Rate to External Sources

Given the lack of a placebo arm in Study 2055, and to provide context to the study results, the Applicant compared the HIV incidence rate observed in this trial to the background HIV infection rate in MSM not in the trial who were at risk of HIV-1 acquisition and not taking PrEP. Based on CDC data from 25 U.S. Metropolitan Statistical Areas (MSAs) that overlapped with Study 2055 sites, the 2016 HIV-1 infection rate in at-risk MSM not using PrEP was 4.02 infections per 100 PY (95% CI 3.56, 3.66). In comparison, the HIV-1 incidence rate at these 25 study sites (using the FAS) was 0.077 infections per 100 PY (95% CI 0.009, 0.278) in the F/TAF group and 0.446 infections per 100 PY (95% CI 0.231, 0.78) in the F/TDF group. In sum, use of F/TAF or F/TDF for PrEP in this trial significantly reduced the HIV-1 incidence rate compared to the background rate in MSM not using PrEP as the upper limits of the 95% CI for the HIV incidence rates in each group were below the lower limit of the 95% CI for the background infection rate.

In addition, the Applicant compared the HIV incidence rates observed in this trial to similar cohorts of MSM at risk of HIV infection based on reported rectal gonorrhea rates, which based on regression modeling are considered to be strongly correlated with HIV infection rates {Mullick and Murray 2019}. Observed rectal gonorrhea incidences rates in Study 2055 (FAS) were 21.6 per 100 PY in the F/TAF group and 20.5 per 100 PY in the F/TDF group. Based on these rates, the HIV-1 incidence rates expected for this trial, in the absence of PrEP, were 6.61 and 6.36 infections per 100 PY in the F/TAF and F/TDF groups, respectively. For each treatment group, the upper limit of the 2-sided 95% exact CI for the observed HIV-1 incidence rate was below the lower limit of the 2-sided 95% prediction band of the HIV-1 incidence rate predicted by the rectal gonorrhea rate, implying the effectiveness of F/TAF or F/TDF for PrEP. Results were similar using the PP analysis set.

Characteristics of Subjects Infected with HIV-1

All 22 HIV-1 infected subjects in Study 2055 were MSM and none were TGW. The median age was 27 years old in this group and 7 (32%) subjects were < 25 years of age. Six (27%) subjects were young MSM of color (i.e., < 25 years of age and black/mixed black or Hispanic/Latino). The median time to HIV diagnosis was 231 days from the time of randomization.

As previously noted, 9 of the 22 subjects with HIV-1 infection prematurely discontinued study drug or had drug interruption prior to their diagnosis (F/TAF 3, F/TDF 6). The median time from discontinuation of PrEP to HIV-1 diagnosis was overall 60 days (range: 20-205 days); by treatment group, the median time was 47 days (range: 46-161 days) in the F/TAF group and 74 days (range: 20-205 days) in the F/TDF group.

As also previously noted, 5 of 22 subjects with HIV-1 infection were suspected of having a baseline infection at the time of randomization (based on blinded medical review of the data). Four of these subjects (all in the F/TDF group) had evidence of genotypic resistance to FTC (i.e., M184I/V), but it is unclear whether resistant virus was transmitted or selected during PrEP use in these cases. Please refer to Section 4.3 of this review and the FDA Virology review by Dr. Deming for further discussion of resistance issues in Study 2055.

Compared to subjects not infected with HIV-1, the 22 subjects with HIV-1 infection had lower self-reported rates of condom use, higher self-reported numbers of unique sex partners, and higher rates of STIs diagnosed during the trial. Most importantly, however, results of the DBS case-control substudy suggested poor adherence to study drug within this group. Although adherence rates by self-report and pill counts were high, median TFV-DP levels on DBS at the time of the HIV-1 diagnosis visits were significantly lower in this group compared with the matched uninfected control subjects.

- Of the 7 subjects in the F/TAF group, 1 subject with high TFV-DP levels was suspected of having a baseline HIV-1 infection, 5 had low TFV-DP levels, and 1 had medium TFV-DP levels.
- Of the 15 subjects in the F/TDF group, 4 subjects with high TFV-DP levels were suspected of having a baseline HIV-1 infection, 10 had low TFV-DP levels, and 1 with a missing DBS sample at the time of the HIV diagnosis visit had high TVF-DP levels as imputed from a sample collected 12 weeks prior.

Baseline and on-treatment characteristics, including adherence data, for the 22 HIV-infected subjects, based on the submitted datasets and subject narratives, are presented in tabular form in Table 11.

<u>Reviewer comment:</u> In the 90-day Safety Update for this application (submitted July 3, 2019), the Applicant reports that an additional subject in the F/TAF group (Subject (b) (6)) was diagnosed with HIV-1 infection on Study Day 678. Per the subject narrative, this 21-year-old black MSM in Atlanta, GA was non-adherent to study drug dosing, as evidenced by DBS sampling. The addition of this subject brings the total number of observed HIV-1 infections in Study 2055 to 23 (F/TAF 8, F/TDF 15) but does not affect the overall conclusion of noninferiority between the two drugs.

Table 11: Characteristics of HIV-1 Infected Subjects – Full Analysis Set (GS-US-412-2055)

Subject ID	Age	Race	Hispanic Latino	Country	Circ	Prior PrEP	Day D/C Study Drug	Days to HIV+	# UIAI 90D	# URAI 90D	Recreational Drug Use	STIs During Trial	Adherence/ Comments
F/TAF													
(b) (6)	24	White	Yes	USA	No	No	363	408	4	0	Yes	CT rectal CT urethral GC urethral	Off study drug at time of infection (Day 386 per subject) due to drug interruption; moderate drug levels on DBS prior to drug interruption
(b) (6)	22	Black	No	USA	No	No	596	596	2	4	No	None	Adherence 61% by pill count; no drug detected by DBS; current partner HIV+ (suspected out of care)
	47	White	No	CAN	No	No	40	29	12	12	Yes	None	Adherence 100% by pill count; "did not wait 7-14 days" after initiating PrEP before having unprotected sex; Week 4 PBMC TFV-DP 838.6 fmol/10^6 cells **Suspected baseline infection*
	27	White	No	GER	Yes	No	74 (subject decision)	234	4	4	Yes	Genital herpes	Off study drug at time of infection
	48	White	Yes	ESP	No	No	589	589	2	0	Yes	None	Poor adherence by DBS; current partner HIV+ (suspected out of care)
	22	White	Yes	ESP	Yes	No	49 (subject decision)	95	3	3	Yes	GC pharyngeal CT urethral	Subject stopped study drug on Day 49; sore throat, nausea, diarrhea, lymphadenopathy on Day 63-69 consistent with acute HIV infection
	20	White	Yes	ESP	No	No	37 (due to AE)	82	0	7	Yes	CT rectal GC rectal GC pharyngeal	Off study drug at time of infection
F/TDF													
	44	White	Yes	USA	No	No	420	420	4	4	No	CT rectal Syphilis	Adherence "just okay"; 83% at Week 48 by CASI; poor adherence by DBS
	25	White	No	USA	Yes	No	168 (due to AE)	372	0	3	Yes	GC rectal GC pharyngeal	Off study drug at time of infection
	25	Native Hawaiian	No	USA	Yes	No	37	37	0	3	Yes	GC rectal	High adherence by pill count, CASI, and DBS on Day 29

Subject ID	Age	Race	Hispanic Latino	Country	Circ	Prior PrEP	Day D/C Study Drug	Days to HIV+	# UIAI 90D	# URAI 90D	Recreational Drug Use	STIs During Trial	Adherence/ Comments
		or Other Pacific Islander										CT rectal Syphilis	**Suspected baseline infection*
(b) (6)	29	White	Yes	USA	No	No	510	506	2	2	No	CT rectal CT pharyngeal CT urethral GC pharyngeal Syphilis	No returned bottles for pill counts; drug undetected by DBS
	32	White	No	USA	Yes	No	90	85	3	9	Yes	GC rectal GC pharyngeal	Adherence 84% by pill count; Week 4 PBMC TFV-DP 25.7 fmol/10^6 cells **Suspected baseline infection*
	24	Black	No	USA	No	No	121 (due to AE)	219	5	0	No	CT rectal GC rectal	Off study drug at time of infection
	37	White	No	USA	Yes	No	334 (subject decision)	420	7	12	No	CT urethral GC urethral Syphilis	Off study drug at time of infection - drug holiday due AE of headache and nausea
	34	White	No	USA	Yes	Yes (not at B/L)	34	29	0	3	Yes	None	Site used 3rd generation rapid tests for screening **Suspected baseline infection*
	19	Black	No	USA	No	No	762	760	4	1	Yes	8 episodes of GC/CT Syphilis	Reported as "just okay"; poor adherence by DBS
	27	Black	No	USA	Yes	No	615	615	1	1	Yes	GC rectal CT rectal Syphilis	Reported as "just okay"; poor adherence by DBS
	18	White	No	CAN	Yes	No	125 (subject decision)	184	0	14	Yes	CT rectal GC rectal	Off study drug at time of infection; poor adherence by DBS prior
	33	White	No	CAN	Yes	No	96 (non-compliance)	126	3	3	No	GC pharyngeal CT urethral	Off study drug at time of infection; poor adherence by DBS prior
	31	White	No	USA	Yes	Yes	476	474	7	6	Yes	GC rectal GC pharyngeal	High adherence by DBS up to Day 425; no DBS data at Day 474

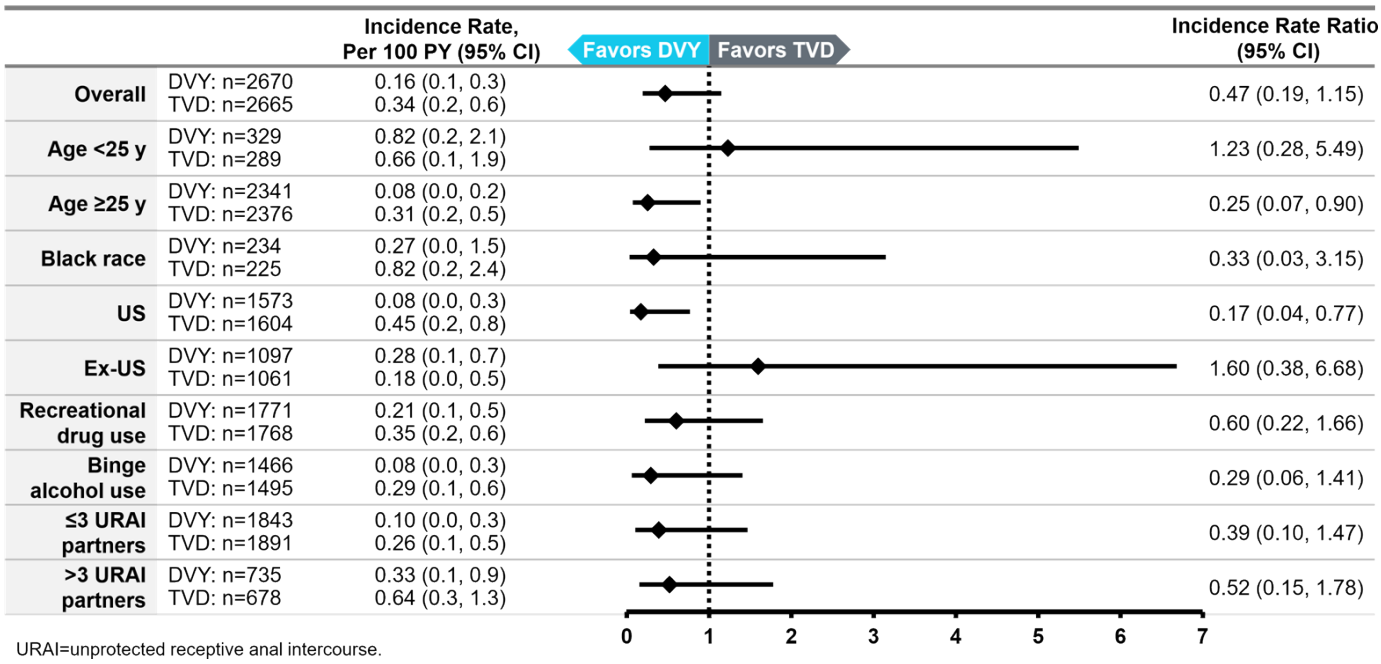
Subject ID	Age	Race	Hispanic Latino	Country	Circ	Prior PrEP	Day D/C Study Drug	Days to HIV+	# UIAI 90D	# URAI 90D	Recreational Drug Use	STIs During Trial	Adherence/ Comments
						(at B/L)						CT rectal Syphilis	
(b) (6)	25	White	No	UK	No	Yes (not at B/L)	209 (non-compliance)	228	3	13	Yes	GC rectal GC pharyngeal CT urethral	Tested HIV+ outside; poor adherence by DBS; "felt ashamed at having not taken his PrEP properly"
	28	Other	No	USA	Yes	No	36	36	25	10	Yes	GC rectal GC pharyngeal	Adherence "just okay"; > 10 RAI partners between Screening and Day 1 **Suspected baseline infection*
TOTALS	Mean 26 Median 27	White 15 Black 5 Native Hawaiian /PI 1 Other 1	Yes 6	USA 14 CAN 3 ESP 3 GER 1 UK 1	No 10 Yes 12	Yes 3 (1 at B/L)	Mean 262.8 Median 146.5	Mean 297.5 Median 231	Mean 7 Median 3	Mean 8.7 Median 3.5	Majority used recreational drugs	All except one had a history of STIs, or STIs during trial, or at time of HIV diagnosis	Overall adherence was poor or subjects off drug when tested HIV+

AE=adverse event; B/L=baseline; Circ=circumcised; CASI=computer-assisted self-interview; CT=*Chlamydia trachomatis*; D/C=discontinue; DBS=dried blood spot; GC=*Neisseria gonorrhoeae*; PBMCs=peripheral blood mononuclear cells; RAI=receptive anal intercourse; STIs=sexually transmitted infections; TFV-DP=tenofovir diphosphate; UIAI=unprotected insertive anal intercourse; URAI=unprotected receptive anal intercourse; 90D=90 days prior to screening
Source: Reviewer's analysis of ADSL dataset and subject narratives

Subgroup Analyses of the Primary Endpoint

Analyses comparing HIV-1 infection rates for prespecified subgroups defined by age, race, region, and baseline risk characteristics showed that F/TAF and F/TDF were similarly effective as PrEP in all subgroups, as the 2-sided 95% exact CIs for the HIV-1 infection rates overlapped between the two treatment groups. Figure 2 displays a forest-plot of the HIV-1 incidence rate ratio for selected subgroups. Only the subgroups of age < 25 years and region ex-U.S. had incidence rate ratios greater than 1, but the 95% CI still covered 1.

Figure 2: HIV-1 Incidence Rate Ratios for Selected Subgroups – Full Analysis Set (GS-US-412-2055)



Source: Applicant's presentation for the August 7, 2019 meeting of the Antimicrobial Drugs Advisory Committee

Data Quality and Integrity

The FDA Office of Scientific Investigations (OSI) performed audits of three clinical sites from Study 2055 (Sites 698, 407, and 12936). These sites were selected for inspection because they were among the highest enrollers of subjects, and thus contributed significantly to the overall efficacy evaluation. On-site inspections demonstrated no significant deficiencies or anomalies at any of the audited sites related to data integrity or human subject protection. The OSI concluded that the data from Study 2055 submitted in support of this application appeared reliable based on the available information.

Efficacy Results – Secondary and other relevant endpoints

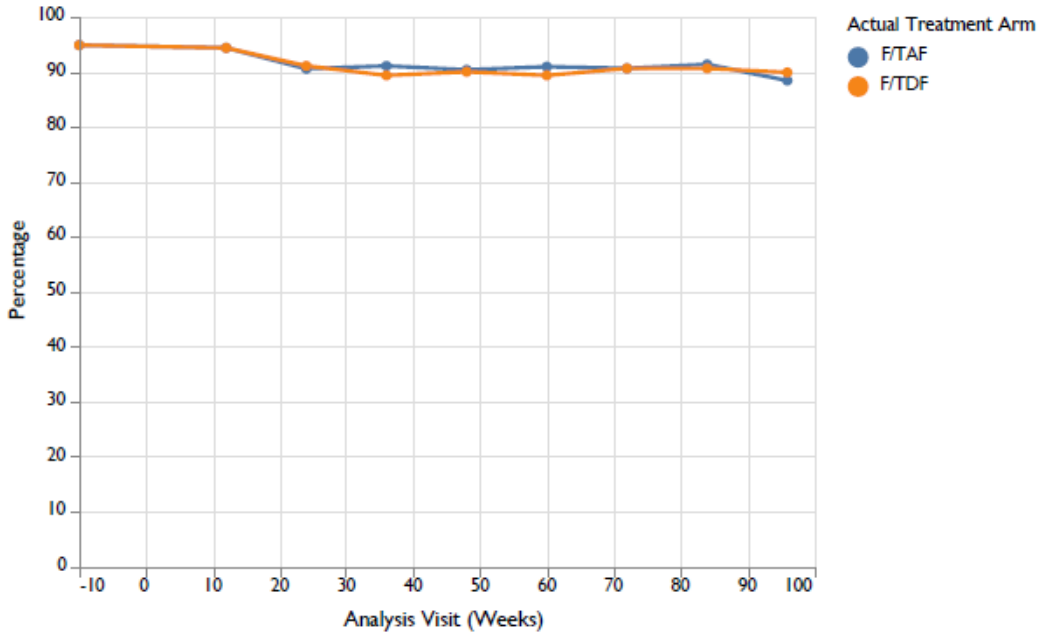
The only secondary endpoint related to efficacy in Study 2055 pertains to the incidence of HIV-1 infection when all subjects have 96 weeks of follow-up in the blinded phase, which has not yet occurred. All other secondary endpoints described in the protocol are related to safety evaluations and are addressed in Section 8.

Among the endpoints of interest, however, are the types and frequency of sexual practices associated with increased risk of HIV-1 infection. While such an endpoint would not be included in product labeling, the frequency of high-risk sexual practices reported during the trial, along with objective STI rates, is important to contextualize the efficacy findings. Given that the HIV-1 infection rates observed in Study 2055 were lower than those in previous PrEP trials in MSM, the finding of similar efficacy between F/TAF and F/TDF in the present trial can either mean that either both drugs were effective in reducing the risk of HIV-1 infection or that neither drug was effective because the study population was not at substantial risk. To that end, in addition to recruiting subjects with high-risk baseline characteristics, it was important to demonstrate that enrolled subjects remained at high risk during the trial for the efficacy results to be considered reliable.

Sexual Risk Behaviors During Study

Based on CASI reporting, the percentage of subjects reporting condomless sex during Study 2055 remained consistently high in both treatment groups (Figure 3).

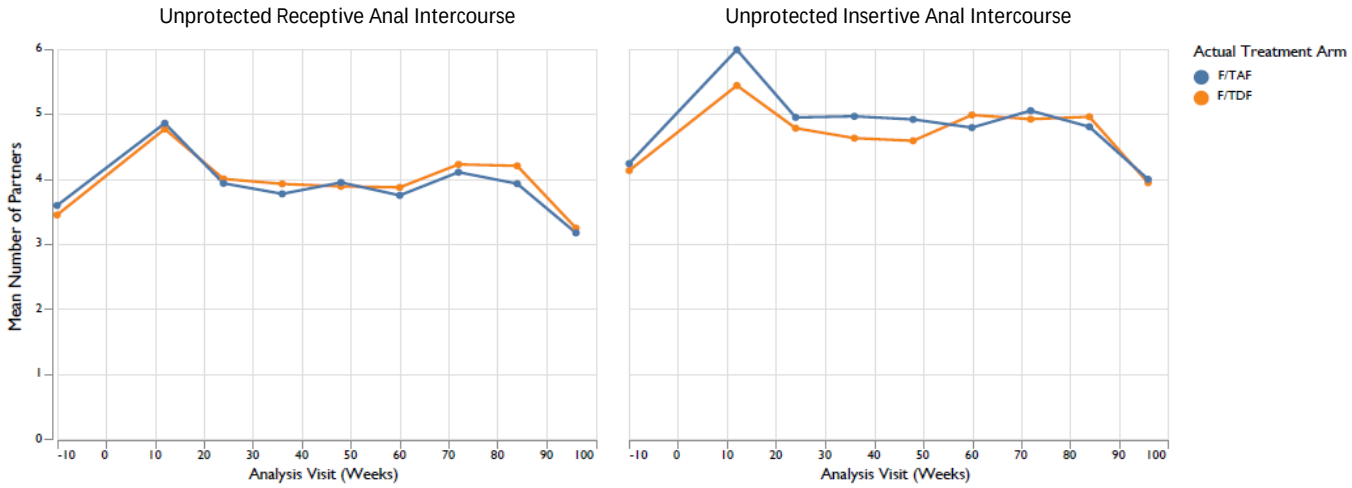
Figure 3: Percentage of Subjects Reporting Condomless Sex Since Last Visit (GS-US-412-2055)



Source: FDA analysis of ADQS dataset – Safety Analysis Set

In addition, the mean number of unique URAI or UIAI partners reported at each study visit remained consistently elevated and similar to screening/baseline reporting (Figure 4).

Figure 4: Mean Number of Unprotected Anal Intercourse Partners Since Last Visit (GS-US-412-2055)



Note: Values for Week 12 are the sum of Week 4 and Week 12 reporting and are therefore higher compared to the self-reported values obtained at 12-week intervals during the remainder of the trial.
Source: FDA analysis of ADSL and ADSQ datasets – Safety Analysis Set

Sexually Transmitted Infections (STIs) During Study

Samples for gonorrhea and chlamydia testing were collected from three anatomic sites (oral , rectal, and urine) at each visit in every subject and analyzed by nucleic acid amplification testing (NAAT). Samples for syphilis testing were collected at each visit and analyzed per local standards.

Based on the proportions of subjects infected with gonorrhea or chlamydia during the trial (57% overall), the rate of sexual risk behavior was high in both treatment groups (Table 12).

Table 12: Gonorrhea and Chlamydia Infections Post-baseline – Full Analysis Set (GS-US-412-2055)

	Number (%) of Subjects		
	F/TAF (N=2670)	F/TDF (N=2665	Total (N=5387)
Gonorrhea or Chlamydia	1505 (56)	1550 (58)	3055 (57)
Rectal	1089 (41)	1135 (43)	2224 (42)
Pharyngeal	838 (31)	821 (31)	1659 (31)

Urethral	420 (16)	417 (16)	837 (16)
Gonorrhea	1053 (39)	1059 (40)	2112 (40)
Rectal	651 (24)	662 (25)	1313 (25)
Pharyngeal	744 (28)	726 (27)	1470 (28)
Urethral	129 (5)	142 (5)	271 (5)
Chlamydia	1049 (39)	1071 (40)	2120 (40)
Rectal	810 (30)	835 (31)	1645 (31)
Pharyngeal	197 (7)	171 (6)	368 (7)
Urethral	335 (13)	324 (12)	659 (12)

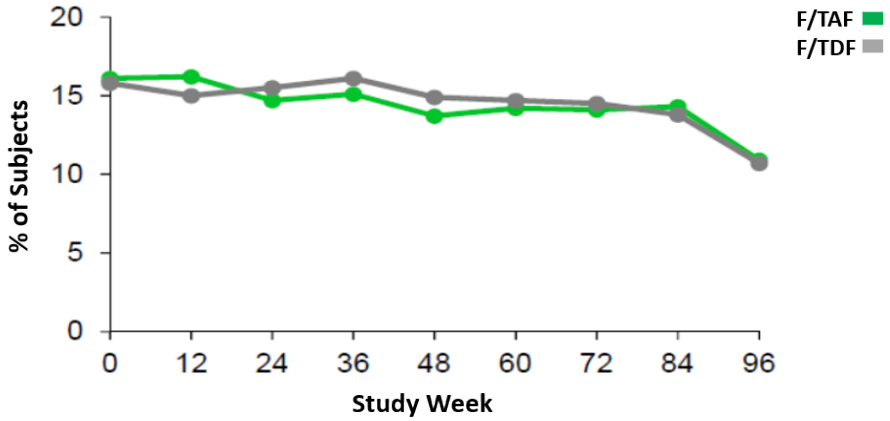
Source: FDA analysis of ADLB dataset

- The incidence rate of gonorrhea in the trial was 47.1/100 PY in the F/TAF group and 45.3/100 PY in the F/TDF group; for rectal gonorrhea, the incidence rates were 21.6/100 PY and 20.5/100 PY, respectively.

- The incidence rate of chlamydia in the trial was 41.9/100 PY in the F/TAF group and 41.6/100 PY in the F/TDF group; for rectal chlamydia, the incidence rates were 27.5/100 PY and 28.2/100 PY, respectively.

Notably, the incidence rates of any gonorrhea or chlamydia infection remained high in both treatment groups throughout the course of the trial, as determined by the number of infections diagnosed during each 12-week period (Figure 5).

Figure 5: Incidence of Any Gonorrhea or Chlamydia Infection Over Time – Full Analysis Set (GS-US-412-2055)



Source: Adapted from Interim Clinical Study Report for GS-US-412-2055 (Figure 13, page160)

Similarly, syphilis was diagnosed in 14% of subjects in either treatment group during the trial, for an incidence rate of 10.3/100 PY in the F/TAF group and 9.5/100PY in the F/TDF group. The majority of syphilis infections were new infections and diagnosed during the primary stage.

> *Reviewer comment:* *Taken together, the post-baseline sexual risk behaviors and STI rates observed in Study 2055 suggest that the population remained at consistently high risk of HIV-1 acquisition throughout the trial. Furthermore, given that these on-treatment observations were not dissimilar to the baseline findings, there was no evidence of risk compensation occurring during the trial.*
>
> *Lastly, the randomized population reported a mean of 4 unique UIAI partners in the 3 months prior to screening. In addition, 92% reported UIAI events during the trial (data not shown) and 16% were diagnosed with chlamydial or gonococcal urethritis. Given these findings, it is reasonable to assume that penile HIV-1 exposures were likely occurring during the trial. While a subgroup analysis by sexual practices was not possible given the trial's eligibility criteria and the large degree of overlap between UIAI and URAI behaviors in most subjects, the low number of observed HIV-1 infections suggests a protective effect of F/TAF and F/TDF for this low-risk exposure category as well.*

Dose/Dose Response

Not applicable as only one dose of F/TAF was evaluated in Study 2055.

Durability of Response

Given the distribution of HIV-1 infection events observed in Study 2055, the protective effect of F/TAF for PrEP appears to be durable over the time the drug is administered.

Persistence of Effect

Based on very limited clinical data in two subjects (i.e., Subjects (b) (6) and (b) (6) in Study 2055 - see Table 11), the protective effect of F/TAF for PrEP does not appear to persist beyond 2 weeks after stopping drug (and may be even shorter). This is at most a conservative estimate based on time of study drug cessation and time of HIV-1 exposure/onset of symptoms as self-reported by these two subjects and should be interpreted with caution.

Using a TFV-DP threshold concentration of 40 fmol/10^6 cells in PBMCs, the Applicant conducted simulations based on PK data from a healthy volunteer trial (Study GS-US-380-4017) and reported that 50% of individuals are expected to have TFV-DP concentrations above this threshold approximately 16 days after cessation of F/TAF taken once daily. This target TFV-DP concentration in PBMCs, however, has not been validated as a surrogate of PrEP efficacy.

In conclusion, the time after cessation of F/TAF for which a protective effect can be expected is not known. Likewise, the time from initiation of F/TAF to maximal protection is not known.

Additional Analyses Conducted on the Individual Trial

None to report.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not applicable as only one clinical trial was submitted to support efficacy in this application.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Study 2055 enrolled a large population of MSM/TGW at high risk of HIV-1 infection and can be therefore relied upon to inform the benefit of F/TAF for PrEP in the postmarket setting in a biological male population at risk from rectal or penile sexual exposure. That said, the trial enrolled a population that was largely reflective of people taking PrEP today and not of people who are at highest risk of new HIV-1 infections right now. There were limited number of TGW, young adults, African-Americans, or elderly subjects, thus limiting the strength of the evidence for these important subpopulations. The effectiveness of F/TAF for PrEP is nonetheless expected to be the same across a diverse biological male population, if individuals are adherent to daily use, because the sexual routes of HIV transmission and the effect of F/TAF to prevent the establishment of HIV-1 infection are the same regardless of age, race or ethnicity. For this reason, and because dosing is the same for adults and adolescents, extrapolating efficacy from this trial to support an indication in a comparable at-risk adolescent population is scientifically valid. Significantly, subgroup analyses in Study 2055, limited though some were by sample size, did not show any efficacy differences across various subgroups.

Another postmarket consideration relates to the use of F/TAF for PrEP in at-risk individuals with renal insufficiency. While Study 2055 did not enroll such subjects, F/TAF is approved for use in PLWH with $eGFR_{CG} \geq 30$ mL/min and there is no reason to suspect that renal safety in uninfected individuals should be any different.

The major concern regarding the benefit of F/TAF in the postmarket setting is the lack of clinical data in cisgender women, or individuals at risk of HIV-1 acquisition from receptive vaginal intercourse. This is particularly concerning given that adult and adolescent women made up 19% of new HIV diagnoses in the U.S. in 2017 {CDC 2018a}. A postmarketing commitment will be issued for the Applicant to collect effectiveness data in this population. Until such data are submitted, however, the PrEP indication for F/TAF will exclude individuals at risk from receptive vaginal sex. Labeling, including a Medication Guide, will explicitly state the lack of effectiveness information in cisgender women to mitigate the potential risk of off-label use. In the interim,

F/TDF remains a safe and effective option for use in this population.

7.2.2. Other Relevant Benefits

The tablet for F/TAF is smaller than the currently marketed PrEP product, F/TDF, and may be considered by some at-risk individuals to be a relevant benefit, thereby potentially improving uptake, adherence and persistence of PrEP use.

7.3. Integrated Assessment of Effectiveness

The clinical trial results of Study 2055, in 5,335 adult MSM/TGW subjects at high risk of HIV-1 infection in the Full Analysis Set, provide substantial evidence of F/TAF efficacy to reduce the risk of HIV-1 acquisition from rectal or penile sexual exposures. Despite the low number of HIV infections observed in the trial, noninferiority of F/TAF to approved F/TDF for PrEP was demonstrated. While there were less HIV-1 infections in the F/TAF group than in the F/TDF group, the trial was not large enough to support any superiority claims of F/TAF over F/TDF.

Of note, the HIV-1 infection rates observed in Study 2055 were lower than those observed in previous clinical trials of oral PrEP in MSM, raising concerns about whether the constancy assumption was maintained. However, several factors suggest that Study 2055 had adequate sensitivity to assess noninferiority. For one, the design of the trial was consistent with previous trials in MSM that demonstrated efficacy of F/TDF over placebo. Secondly, the enrolled population was at considerable risk for HIV-1 infection during the trial based on their sexual risk behaviors (as determined by self-reporting and laboratory-based STI rates) and the high HIV-1 incidence rates in their communities (as determined by background HIV-1 infection rates among MSM not taking PrEP). Given these observations, the likeliest explanation for the low number of HIV infections in Study 2055 was the high level of adherence to study drug reported in each arm, as it has been established that PrEP efficacy is strongly correlated with adherence.

Resistance was not observed among subjects infected with HIV-1 in the F/TAF group, and what resistance was observed in the F/TDF group (n=4) occurred in subjects suspected of having a baseline infection. The numbers of HIV-1 infections in Study 2055 were too small to draw any conclusions regarding the relative risk of resistance.

In conclusion, the submitted efficacy data from Study 2055 are robust to support a PrEP indication for F/TAF in adult MSM/TGW at high risk of HIV-1 acquisition from rectal or penile sexual exposure. Extrapolation of these data to support an indication in a comparable adolescent population at risk is acceptable. However, the data in MSM/TGW are not adequate to support an indication in cisgender women given the different sites of HIV-1 exposure between the two populations and the uncertainty regarding the role of mucosal tissue drug concentrations to PrEP efficacy. As such, contrary to the Applicant's proposal, the indication for

F/TAF for PrEP will exclude individuals at risk of HIV-1 infection from receptive vaginal sex.

8. Review of Safety

8.1. Safety Review Approach

Clinical trial data from the pivotal Study 2055 in MSM/TGW formed the basis of the safety review for this application. These data were submitted as SAS transport (.xpt) files and independently analyzed by this reviewer using the following tools: JMP®, JMP® Clinical, JReview® and the MedDRA-Based Adverse Event Diagnostics (MAED) tool developed by CDER.

No new safety issues specific to F/TAF were identified during the TAF for PrEP development program. The following issues were evaluated in greater detail based on the known safety profiles of F/TAF and F/TDF: renal safety, bone safety, and fasting serum lipids.

The clinical data from Study 2055 submitted on April 5, 2019, with an analyses data cut date of January 31, 2019, were used for all safety analyses described in this review. Although 24 women were exposed to F/TAF at the 200/25 mg dose in the external Study A15-137, data from these subjects were excluded because of the limited duration of exposure (14 days).

The Applicant also submitted a 90-Day Safety Update on July 3, 2019, but the updates were minimal compared to the original data submitted with the sNDA and did not alter the safety conclusions. Thus, only the original safety data are described here.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The Safety Analysis Set, which included all subjects randomized into Study 2055 and who received at least 1 dose of study drug, was used for all the safety analyses described in this review. Given the large sample size needed to evaluate PrEP efficacy, the total number of individuals exposed to F/TAF in Study 2055 (Table 13) exceeded the minimum specified in the ICH E1A guideline recommendations.

Table 13: Safety Database for F/TAF for HIV-1 PrEP Indication

Safety Database for the Study Drug[1] Individuals exposed to any treatment in this development program for the indication under review N=5387 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	F/TAF (N=2694)	F/TDF (N=2693)	Placebo (N=0)

Healthy volunteers	0	0	0
Controlled trials conducted for this indication	2694	2693	0
All other trials conducted for this indication	N/A	N/A	N/A
Controlled trials conducted for other indications	N/A	N/A	N/A

[1] *Study drug* means the drug being considered for approval.

As of the primary analysis data cut date, median (Q1, Q3) exposure to the study drugs was as follows: F/TAF 85.7 (83.7, 96.7) weeks, F/TDF 86.7 (83.9, 96.6) weeks. These correlated to 4,318.9 and 4,338.7 person-years of exposure to F/TAF and F/TDF, respectively. Table 14 displays the exposure to F/TAF in Study 2055 by various duration cut-offs.

Table 14: Duration of Exposure to F/TAF (GS-US-412-2055)

	Number of patients exposed to the study drug: 2694				
	>= 4 weeks	>=24 weeks	>=48 weeks	>=72 weeks	>=96 weeks
F/TAF	N=2654 (99%)	N=2508 (93%)	N=2394 (89%)	N=2287 (85%)	N=906 (34%)

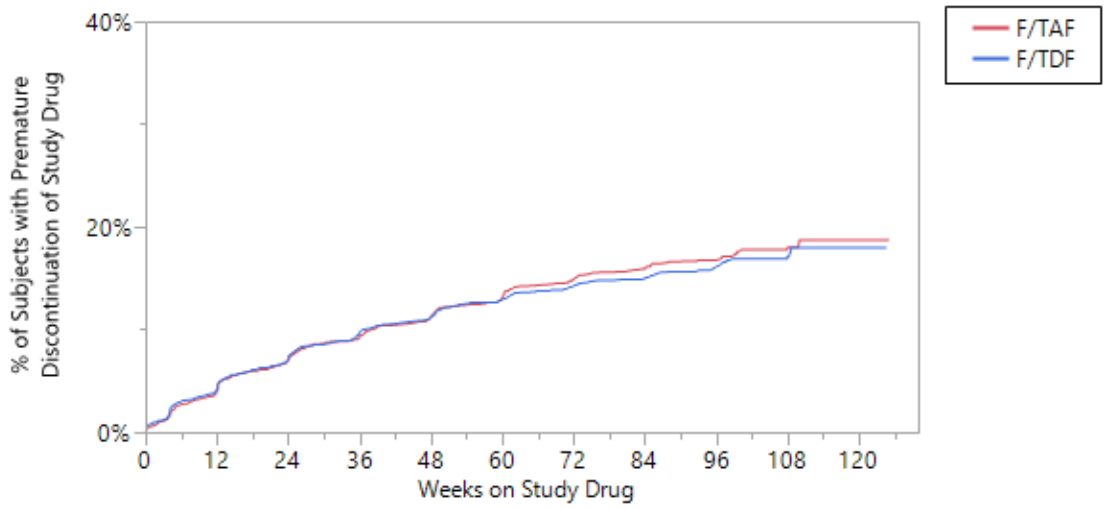
Source: Adapted from Interim Clinical Study Report for GS-US-412-2055 (Table 24, page 124)

The median (Q1, Q3) durations of study drug holidays and/or interruptions through the primary analysis data cut date were as follows:

- Drug holidays: F/TAF (N=32) 12.1 (9.3, 14.1) weeks; F/TDF (N=19) 12.3 (9.6, 22.1) weeks
- Drug interruptions: F/TAF (N=746) 1.1 (0.4, 3.7) weeks; F/TDF (N=751) 1.3 (0.4, 4) weeks

There was no statistically significant difference between the two treatment groups in the overall Kaplan-Meier estimate of time to premature discontinuation of study drug (Figure 6).

Figure 6: Time to Premature Discontinuation of Study Drug, Kaplan-Meier Estimate (GS-US-412-2055)



Source: Reviewer's analysis of ADLS dataset

8.2.2. Relevant characteristics of the safety population:

Refer to Section 6.1.2 for demographic and other baseline characteristics of the safety population. In general, the treated population of Study 2055 was consistent with one at substantial risk of acquiring HIV-1. However, the range of subpopulations at risk of infection, such as transgender women, persons of color, young adults (<2 5 years of age) or the elderly (≥ 65 years of age), many of whom make up the target U.S. population for PrEP implementation and are thus reasonably expected to use the product, was not well represented. While these issues may limit the generalizability of the safety findings from Study 2055, the clinical experience with F/TAF for the treatment of HIV-1 supports its safe use across a broad range of subpopulations defined by age, race, or gender.

8.2.3. Adequacy of the safety database:

The safety database, consisting of 2,694 subjects with a median of duration of exposure to F/TAF of 86 weeks, is extensive and adequate to assess the safety of once-daily F/TAF for a PrEP indication in the intended U.S. population, with the limitations noted above.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no issues identified regarding data integrity. For Study 2055, the narratives for deaths, serious adverse events, treatment discontinuations, and adverse events of interested were reviewed and found to be consistent with the Applicant's summary and assessment. Three clinical sites that participated in Study 2055 were audited by OSI. The on-site inspections demonstrated no significant findings at any of the audited sites related to data integrity.

The quality of the submission itself (e.g., completeness, organization, and ease of finding information) was adequate to allow for the safety review be conducted in a timely manner.

8.3.2. Categorization of Adverse Events

The Applicant provided accurate definitions of AEs and serious adverse events (SAEs) for events reported in Study 2055. An AE was defined as any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not considered related to study drug. Pre-existing events that increased in severity or changed in nature during or as a consequence of participation in the trial were also considered AEs. An SAE was defined as any event that results in death, life-threatening, hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or a medically important event or reaction.

All SAEs were collected from the time the informed consent was signed through the duration of the trial, including the protocol-required post treatment follow-up period. All AEs following the initiation of study drug until 30 days after last administration of study drug were reported in the eCRF; AEs that occurred after informed consent, but prior to initiation of study drug, were reported if they were related to protocol-mandated procedures. All AEs were followed until resolution or until the AE was stable, if possible.

A treatment-emergent AE (TEAE) was defined as 1) any AE with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of the study drug (regardless of study drug interruptions), or 2) any AE leading to premature discontinuation of study drug. The Applicant's definition of a TEAE is reasonable based on the known safety profile of the study drugs.

The relationship or association of an AE to study drug was assessed by site investigators using clinical judgment. An AE was considered related if there was a reasonable possibility that the event was caused by study drug and no evidence of an alternative etiology.

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 was used for the coding of AEs. All levels of the MedDRA hierarchy were provided for each AE in the AE dataset; i.e., System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), And Lowest-Level Term (LLT). Verbatim terms were included in the data files and the Applicant's translation of verbatim terms to MedDRA Preferred Terms was appropriate. An AE dictionary and the process by the which the Applicant mapped verbatim terms to preferred terms was provided with the application.

All AEs and laboratory results were recorded according to uniform guidelines and graded by site investigators as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life-threatening) according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities specified in the study protocol. For AEs related to laboratory abnormalities, the event was graded based on the clinical severity in the context of the underlying conditions.

Adverse events were assessed by frequency (i.e., events per subject), which is acceptable and commonly done for antiviral drug products. In general, the Applicant performed its safety analyses at the MedDRA PT level, but summarized results by SOC, HLT, PT, and treatment group. There is an inherent risk to this method as it may diminish safety signals by "splitting" similar preferred terms. This reviewer therefore also conducted comparative analyses at higher MedDRA hierarchy levels and used Standardized MedDRA Queries (SMQs) when appropriate. For instance, the Applicant identified diarrhea, nausea, and abdominal pain as gastrointestinal AEs of interest because they are common events following initiation of F/TAF and F/TDF for

PrEP; however, the Applicant only used the specific MedDRA PTs to identify these events. For abdominal pain in particular, this method excludes several related PTs under the same MedDRA HLT and underestimates the true frequency of the event.

Proximal renal tubulopathy (PRT) was another AE of interest, relevant because of the potential risk associated with F/TDF use. For its analysis of PRT events, the Applicant identified cases based on the investigator-reported PTs of Fanconi syndrome, Fanconi syndrome acquired, renal tubular disorder, renal tubular dysfunction, and renal tubular injury. While these terms were deemed acceptable by this reviewer, relying on investigator reporting alone may be subject to reporting bias. Therefore, this reviewer also analyzed potential cases of PRT using objective laboratory-based criteria (see Section 8.5.1).

8.3.3. Routine Clinical Tests

Routine clinical evaluations and laboratory testing occurred at pre-specified regular intervals at Weeks 4 and 12, and every 12 weeks thereafter. Safety assessments included monitoring of AEs and concomitant medications, physical examinations, weight, vital signs measurements (blood pressure, pulse, respiration rate, and temperature), and clinical laboratory tests (hematology, chemistry, urinalyses including markers of renal function, STIs, HCV, and HBV). All routine clinical laboratory data were processed at a central laboratory. In a subset of subjects, DXA scans of the hip and spine were performed at Day 1 and Weeks 48 and 96 to assess BMD. The frequency and scope of the testing were deemed acceptable.

Treatment-emergent laboratory abnormalities were defined as values that increased at least 1 toxicity grade from baseline at any postbaseline time point up to 30 days after permanent discontinuation of study drug. A baseline laboratory value was defined as the last nonmissing value on or prior to the date of first dose of study drug. If there were multiple records on the same day or no time recorded on the same day, the value with the lowest severity was chosen for baseline (or an average for numeric observations). For postbaseline visits, the worst severity value within the window was selected (i.e., abnormal was selected over normal).

Fasting was recommended for postbaseline lipid assessments but not required for screening; therefore, fasting status at baseline was approximately half fasting and half non-fasting, and whether a postbaseline abnormality was treatment emergent or not could not be determined for approximately half of the subjects. Because of this, maximum postbaseline grade was summarized instead of treatment-emergent grade for non-fasting glucose (including glucose results without a known fasting status), fasting glucose, fasting total cholesterol, fasting triglycerides, and fasting LDL.

8.4. Safety Results

8.4.1. Deaths

There were two treatment-emergent deaths in Study 2055, one in each treatment group. Neither death was considered related to study drug by the investigators.

- Subject (b) (6) (F/TAF) – 42-year-old man (U.S.) died due to a hit and run car accident on Study Day 203.
- Subject (b) (6) (F/TDF) – 26-year-old man (U.S.) died due to unknown causes on Study Day 20. No autopsy was performed.

In addition, there was one nontreatment-emergent death in a 52-year-old man in the F/TDF group (Subject (b) (6)) who died due to metastatic squamous cell carcinoma. The death occurred 54 days after the last dose of study drug and was not considered related to drug.

8.4.2. Serious Adverse Events

The overall incidence of treatment-emergent SAEs in Study 2055 was 6% (F/TAF 6%, F/TDF 5%). There were no major differences between the treatment groups with respect to the incidence, severity, or types of SAEs reported (regardless of MedDRA hierarchy terms). The most common SAEs (reported in more than 2 subjects) were:

- F/TAF: appendicitis (0.3%), suicidal ideation (0.3%), acute kidney injury and hepatitis A (0.2% each), and suicide attempt, depression, cellulitis, pneumonia, and road traffic accident (0.1% each)
- F/TDF: appendicitis (0.3%), suicidal ideation (0.2%), and atrial fibrillation, cellulitis, chest pain, pneumonia, anal abscess, and diverticulitis (0.1% each).

Table 15 lists all the SAEs that occurred in more than one subject in either treatment group.

Table 15: Treatment-Emergent Serious Adverse Events Reported in At Least 2 Subjects in Either Treatment Group (GS-US-412-2055)

MedDRA System Organ Class	*MedDRA Dictionary-derived Term*	*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)
	Total	169 (6)	138 (5)
Blood and lymphatic system disorders		3 (0.1)	4 (0.2)
	Lymphadenitis	0	2 (0.1)
Cardiac disorders		8 (0.3)	10 (0.4)
	Acute myocardial infarction	2 (0.1)	1 (<0.1)
	Atrial fibrillation	2 (0.1)	4 (0.2)
	Myocardial infarction	1 (<0.1)	2 (0.1)
	Supraventricular tachycardia	2 (0.1)	0

Ear and labyrinth disorders		2 (0.1)	0
	Sudden hearing loss	2 (0.1)	0
Endocrine disorders		2 (0.1)	0
Gastrointestinal disorders		18 (1)	12 (1)
	Anal fistula	0	2 (0.1)
	Colitis	2 (0.1)	1 (<0.1)
	Constipation	2 (0.1)	0
	Diarrhoea	1 (<0.1)	2 (0.1)
	Pancreatitis	0	2 (0.1)
General disorders and administration site conditions		7 (0.3)	7 (0.3)
	Chest pain	2 (0.1)	4 (0.2)
	Pyrexia	2 (0.1)	0
Hepatobiliary disorders		2 (0.1)	4 (0.2)
	Cholecystitis	2 (0.1)	2 (0.1)
Infections and infestations		57 (2)	49 (2)
	Anal abscess	1 (<0.1)	3 (0.1)
	Appendicitis	8 (0.3)	9 (0.3)
	Cellulitis	4 (0.2)	4 (0.2)
	Diverticulitis	1 (<0.1)	3 (0.1)
	Gastroenteritis	2 (0.1)	2 (0.1)
	Gastroenteritis shigella	2 (0.1)	0
	Hepatitis A	5 (0.2)	1 (<0.1)
	Influenza	2 (0.1)	1 (<0.1)
	Orchitis	2 (0.1)	0
	Pneumonia	4 (0.2)	4 (0.2)
	Scrotal abscess	2 (0.1)	0
	Sepsis	2 (0.1)	1 (<0.1)
	Tonsillitis	0	2 (0.1)
	Urinary tract infection	0	2 (0.1)
Injury, poisoning and procedural complications		28 (1)	17 (1)
	Ankle fracture	2 (0.1)	0
	Concussion	0	2 (0.1)
	Foot fracture	1 (<0.1)	2 (0.1)
	Overdose	2 (0.1)	1 (<0.1)
	Post procedural haemorrhage	2 (0.1)	1 (<0.1)
	Radius fracture	0	2 (0.1)
	Road traffic accident	4 (0.2)	0
	Tendon rupture	2 (0.1)	0
	Toxicity to various agents	1 (<0.1)	2 (0.1)
Investigations		0	2 (0.1)
Metabolism and nutrition disorders		4 (0.2)	2 (0.1)
Musculoskeletal and connective tissue disorders		6 (0.2)	8 (0.3)
	Osteoarthritis	0	2 (0.1)
	Rhabdomyolysis	2 (0.1)	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)		9 (0.3)	3 (0.1)
	Prostate cancer	2 (0.1)	0
Nervous system disorders		16 (1)	10 (0.4)
	Syncope	2 (0.1)	2 (0.1)
Psychiatric disorders		22 (1)	15 (1)
	Depression	4 (0.2)	1 (<0.1)
	Panic attack	2 (0.1)	0
	Psychotic disorder	2 (0.1)	2 (0.1)
	Suicidal ideation	7 (0.3)	5 (0.2)
	Suicide attempt	4 (0.2)	1 (<0.1)
Renal and urinary disorders		8 (0.3)	8 (0.3)
	Acute kidney injury	5 (0.2)	2 (0.1)
	Nephrolithiasis	2 (0.1)	2 (0.1)
Reproductive system and breast disorders		2 (0.1)	3 (0.1)
Respiratory, thoracic and mediastinal disorders		2 (0.1)	3 (0.1)
Surgical and medical procedures		0	3 (0.1)
Vascular disorders		3 (0.1)	0
	Deep vein thrombosis	2 (0.1)	0

Source: Reviewer's analysis of ADAE dataset

The vast majority (97%) of SAEs were not considered related to study drug by the investigators; the percentage of subjects with study-drug related SAES was low in both treatment groups (F/TAF 3 [0.1%], F/TDF 5 [0.2%]). Most (82%) SAEs were described as moderate to severe (Grade 2-3), while 11% were considered life-threatening (Grade 4). Of the latter, only two (out of 45) events were considered related to study drug: agranulocytosis and pyrexia, both occurring in Subject (b) (6) in the F/TAF group. The subject's narrative is as follows:

- Subject (b) (6) (F/TAF): This 38-year-old man (Germany) experienced sudden fever and vomiting on Study Day 27 while on a business trip to Switzerland. He was hospitalized the following day and febrile neutropenia was diagnosed (WBC 2.2 x10^9 [reference range 4.0-11 x10^9]; neutrophil count 0.13 x10^9 [reference range 1.5-7.5 x10^9]), neutrophils 6.0% [reference range 33.0-75.0%]). Study drug was withdrawn, and the subject received granulocyte colony stimulating factor for two days and intravenous cefepime for six days. An extensive infectious and rheumatologic evaluation was negative. The event was considered resolved by Study Day 33, when he was discharged. Labs obtained two days later showed a neutrophil count of 4.69 x10^9 (or 32%). The subject remained in the trial, but study drug was not resumed. Of note, per a MedWatch report dated 10/06/2017 and submitted to IND 127728, this subject had a history of substance use (gamma-hydroxybutyrate [GHB], ketamine and cannabis) within the last 4 months. The investigator considered the SAE of neutropenic fever related to study drug as the event occurred soon after initiation of treatment and there were no other new medications. The hospital pharmacologist concurred with this assessment because the subject had used GHB and ketamine a few months before without any adverse effect on

WBC counts; hence, a drug interaction seemed unlikely. The Applicant considered that the purity of the illicit drugs in this case could not be ascertained and therefore might provide alternative causality.

Reviewer comment: Per the Applicant, there have been two reports of febrile neutropenia in the TAF development program. Both cases occurred in HIV-1 treatment trials in subjects with hematologic malignancies receiving chemotherapy (see correspondence of June 26, 2019 [NDA 208215, SN 0108]). Given the above subject's use of illicit substances, this reviewer concurs that causality for this SAE cannot be fully ascertained.

A total of 9 subjects (F/TAF 4, F/TDF 5) discontinued study drug because of an SAE, including one subject in the F/TDF group (Subject (b) (6)) with an SAE of acute kidney injury (AKI). This reviewer did not discern any pattern with respect to SAEs leading to drug discontinuation. (Renal AEs are discussed in more detail in Section 8.5.1).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In Study 2055, 85 (2%) subjects permanently discontinued study drug due to a TEAE: F/TAF 36 (1%), F/TDF 49 (2%). No specific TEAE (regardless of MedDRA hierarchy term) was reported in more than 0.2% of subjects in either treatment group. There were no major differences between treatment arms with respect to types, severity or timing of TEAEs that led to drug discontinuation (median time to event was 83 and 93 days for F/TAF and F/TDF, respectively). In both groups, gastrointestinal (GI) disorders were the most common reasons for drug discontinuation. The majority (> 80%) of TEAEs were mild or moderate in severity; review of the Grade 3-4 events did not reveal any new safety concerns for F/TAF or F/TDF. Table 16 lists all TEAEs that led to study drug discontinuation in more than 1 subject in either arm (note: all renal and rash events are listed and TEAEs related to abdominal pain are grouped together).

Table 16: Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation Reported in At Least 2 Subjects Overall (GS-US-412-2055)

MedDRA System Organ Class	*MedDRA Preferred Term*	*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)
	Total	36 (1.3)	49 (1.8)
Cardiac disorders		3 (0.1)	0
Eye disorders		2 (0.1)	0
Gastrointestinal disorders		8 (0.3)	17 (0.6)
	Diarrhoea	4 (0.1)	6 (0.2)
	Nausea	4 (0.1)	4 (0.1)
	Vomiting	2 (0.1)	3 (0.1)
	Abdominal pain*	2 (0.1)	5 (0.2)
	Flatulence	1 (<0.1)	1 (<0.1)
	Abdominal distension	0	2 (0.1)

General disorders and administration site conditions		4 (0.1)	9 (0.3)
	Fatigue	2 (0.1)	6 (0.2)
	Hyperthermia	0	2 (0.1)
Investigations		4 (0.1)	3 (0.1)
	Blood creatinine increased	3 (0.1)	1 (<0.1)
Metabolism and nutrition disorders		3 (0.1)	2 (0.1)
	Alcohol intolerance	1 (<0.1)	1 (<0.1)
	Decreased appetite	1 (<0.1)	1 (<0.1)
Musculoskeletal and connective tissue disorders		4 (0.1)	3 (0.1)
	Back pain	1 (<0.1)	1 (<0.1)
	Osteoporosis	2 (0.1)	0
Nervous system disorders		7 (0.3)	6 (0.2)
	Dizziness	2 (0.1)	1 (<0.1)
	Headache	1 (<0.1)	4 (0.1)
Psychiatric disorders		3 (0.1)	7 (0.3)
	Anxiety	2 (0.1)	2 (0.1)
	Depression	1 (<0.1)	1 (<0.1)
	Insomnia	0	2 (0.1)
Renal and urinary disorders		2 (0.1)	6 (0.2)
	Acute kidney injury	2 (0.1)	2 (0.1)
	Fanconi syndrome acquired	0	1 (<0.1)
	Proteinuria	0	1 (<0.1)
	Renal cyst	0	1 (<0.1)
	Renal impairment	0	2 (0.1)
Skin and subcutaneous tissue disorders		5 (0.2)	4 (0.1)
	Acute generalised exanthematous pustulosis	1 (<0.1)	0
	Erythema	1 (<0.1)	0
	Pruritus generalised	0	1 (<0.1)
	Rash	2 (0.1)	3 (0.1)
	Rash generalised	1 (<0.1)	0

* For this analysis, 'abdominal pain' includes the following MedDRA preferred terms: abdominal pain, abdominal pain upper, and abdominal discomfort.
Source: Reviewer's analysis of ADAE dataset

Compared to drug discontinuations, a greater number of subjects *interrupted* study drug due to a TEAE: F/TAF 151 (6%), F/TDF 138 (5%). The most common events leading to drug interruption were also GI-related, with similar rates in both groups (by MedDRA SOC *Gastrointestinal disorders*: F/TAF 40 [1.5%], F/TDF 35 [1.3%]). For other TEAEs leading to drug interruption, there were no differences between the groups with respect to the incidence or types of events. The median (Q1, Q3) duration of drug interruption was comparable between the groups: F/TAF 14 (5, 32) days, F/TDF 20 (8, 49) days. Seven subjects (F/TAF 4 [0.1%], F/TDF 3 [0.1%]) interrupted due to renal failure/impairment. (Renal AEs are discussed in further detail in

Section 8.5.1.)

A review of safety data in treated subjects who dropped out of the trial for stated reasons other than an adverse event (F/TAF 416 [15%], F/TDF 381 [14%]) did not reveal any imbalances between the two treatment groups or new safety concerns compared with the general safety population. The most common TEAEs in this group, as in the larger study population, were related to infections/infestations and GI disorders. The only TEAEs (by MedDRA PT) within this group that occurred more frequently in the F/TAF arm (risk difference >2.5 per 100) were upper respiratory infection (F/TAF 36/416 [9%], F/TDF 16/381 [4%]) and diarrhea (F/TAF 48/416 [12%], F/TDF 34/381 [9%]).

8.4.4. Significant Adverse Events

The majority (77%) of TEAEs in Study 2055 were Grade 1. The proportion of subjects with Grade 2-4 TEAEs was 47% and 45% in the F/TAF and F/TDF groups, respectively. By MedDRA SOC, the most common (reported in > 5% of subjects) Grade 2-4 TEAEs were infections, gastrointestinal, injury, psychiatric, and musculoskeletal disorders. In both arms, the most common Grade 2-4 TEAEs were related to STIs. A review of specific TEAEs by lower MedDRA hierarchy terms revealed no major differences between the two treatment groups in the frequencies of events (i.e., risk differences were ≤ 1 per 100). Table 17 displays the Grade 2-4 TEAEs that occurred in at least 2% of subjects in either treatment group.

Table 17: Treatment-Emergent Adverse Events Grade 2-4 Reported in At Least 2% of Subjects in Either Treatment Group (GS-US-412-2055)

MedDRA System Organ Class	*MedDRA Preferred Term*	*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)
	Total	1259 (47)	1212 (45)
Infections and infestations		878 (33)	807 (30)
	Anal chlamydia infection	227 (8)	224 (8)
	Oropharyngeal gonococcal infection	201 (8)	209 (8)
	Proctitis gonococcal	206 (8)	191 (7)
	Syphilis	137 (5)	118 (4)
	Urethritis chlamydial	74 (3)	58 (2)
	Urethritis gonococcal	61 (2)	57 (2)
	Upper respiratory tract infection	59 (2)	50 (2)
	Pharyngeal chlamydia infection	45 (2)	47 (2)
	Urethritis	42 (2)	37 (1)
Gastrointestinal disorders		272 (10)	225 (8)
	Diarrhoea	67 (3)	55 (2)
Injury, poisoning and procedural complications		199 (7)	192 (7)
	Exposure to communicable disease	73 (3)	86 (3)
Psychiatric disorders		129 (5)	123 (5)

	Depression	43 (2)	37 (1)
Musculoskeletal and connective tissue disorders		122 (5)	124 (5)

Source: Reviewer's analysis of ADAE dataset

Severe and life-threatening (Grades 3-4) TEAEs were reported in 6% of subjects in both arms; Grade 4 TEAEs were limited to 1% of the safety population. By MedDRA PT, no specific Grade 3-4 event was reported in more 0.3% of subjects in either treatment arm, and the majority (94%) of these TEAEs were not considered related to study drug by the investigators. The most common Grade 3-4 TEAEs were related to suicidal and self-injurious behaviors (by MedDRA HLGT: F/TAF 13 [0.5%], F/TDF 7 [0.3%]), followed by appendicitis (0.2% each arm) and diarrhea (F/TAF 0.1%, F/TDF 0.2%). Given these low frequencies, no differences could be discerned between the groups with respect to severe or life-threatening TEAEs. Table 18 lists the Grade 3-4 TEAEs reported in more than 2 subjects in either treatment group.

Table 18: Treatment-Emergent Adverse Events Grade 3-4 Reported in More Than 2 Subjects in Either Treatment Group (GS-US-412-2055)

MedDRA System Organ Class	*MedDRA Preferred Term*	*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)
	Total	167 (6)	153 (6)
	Grade 3 TEAEs	146 (5)	138 (5)
	Grade 4 TEAEs	21 (1)	15 (1)
Infections and infestations		49 (2)	37 (1)
	Appendicitis	6 (<1)	6 (<1)
	Hepatitis A	4 (<1)	2 (<1)
	Pneumonia	4 (<1)	1 (<1)
	Cellulitis	3 (<1)	1 (<1)
	Gastroenteritis	3 (<1)	1 (<1)
	Influenza	1 (<1)	3 (<1)
Psychiatric disorders		24 (1)	18 (1)
	Suicidal ideation	9 (<1)	4 (<1)
	Suicide attempt	4 (<1)	2 (<1)
	Depression	4 (<1)	2 (<1)
Gastrointestinal disorders		24 (1)	17 (1)
	Diarrhoea	2 (<1)	6 (<1)
	Nausea	4 (<1)	0
Injury, poisoning and procedural complications		23 (1)	15 (1)
	Road traffic accident	5 (<1)	0
Investigations		8 (<1)	18 (1)
	Amylase increased	2 (<1)	3 (<1)
	Lipase increased	1 (<1)	2 (<1)
	Weight decreased	1 (<1)	3 (<1)
Renal and urinary disorders		12 (<1)	7 (<1)
	Acute kidney injury	3 (<1)	1 (<1)

	Nephrolithiasis	3 (<1)	1 (<1)
Cardiac disorders		7 (<1)	8 (<1)
	Atrial fibrillation	2 (<1)	3 (<1)
Blood and lymphatic system disorders		6 (<1)	4 (<1)
	Anemia	2 (<1)	3 (<1)
Musculoskeletal and connective tissue disorders		4 (<1)	10 (<1)
	Rhabdomyolysis	3 (<1)	0
General disorders and administration site conditions		6 (<1)	8 (<1)
	Chest pain	1 (<1)	3 (<1)

Source: Reviewer's analysis of ADAE dataset

Five cases of Grade 3 increased amylase (three with corresponding Grade 3 elevations in lipase) were reported in Study 2055 (F/TAF 2 [0.1%], F/TDF 3 [0.1%]). None of the events was serious and 4 of 5 cases were not considered related to study drug by the investigators. Review of subject-level data for these 5 cases did not reveal any patterns that would be of concern to the use of F/TAF or F/TDF for HIV-1 PrEP.

A total of 4 cases of rhabdomyolysis were reported in Study 2055 (F/TAF 3 [0.1%], F/TDF 1 [<0.1%]), two of which were serious and three of which were severe (Grade 3). None of the cases was considered related to study drug by the investigators, as each case had a plausible alternative etiology for the event.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent Adverse Events

Treatment-emergent adverse events were reported in 93% of subjects overall. Sexually-transmitted infections were the most common TEAEs, with chlamydial and gonococcal infections reported in 41% and 43% of subjects, respectively. Infections aside, the most common TEAEs were diarrhea, nausea, headache, and fatigue. The incidence rates for all TEAEs, regardless of MedDRA hierarchy, were comparable between the two treatment groups, with only "upper respiratory tract infections" (by MedDRA HLT) and "pharyngitis" (by MedDRA PT) having a ≥ 2% risk difference between the arms (in both cases, the risk difference was 2 per 100 and the incidence was higher in the F/TAF group). This reviewer also conducted a comparative analysis of TEAEs by SMQs, broad and narrow, and again found no significant differences between the two groups. Table 19 lists the most common (incidence ≥ 5%) TEAEs reported in the Study 2055.

Table 19: Treatment-Emergent Adverse Events Reported in At Least 5% of Subjects in Either Treatment Group (GS-US-412-2055)

MedDRA High Level Term	*MedDRA Preferred Term*	*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)

	Total	2498 (93)	2494 (93)
Chlamydial infections		1089 (40)	1113 (41)
	Anal chlamydia infection	770 (29)	792 (29)
	Urethritis chlamydial	280 (10)	259 (10)
	Pharyngeal chlamydia infection	175 (7)	149 (6)
Neisseria infections		1167 (43)	1164 (43)
	Oropharyngeal gonococcal infection	740 (28)	722 (27)
	Proctitis gonococcal	693 (26)	671 (25)
	Urethritis gonococcal	216 (8)	210 (8)
	Exposure to communicable disease	465 (17)	441 (16)
	Diarrhoea	430 (16)	422 (16)
	Upper respiratory tract infection	356 (13)	310 (12)
	Nasopharyngitis	350 (13)	355 (13)
	Syphilis	342 (13)	321 (12)
	Nausea	196 (7)	187 (7)
	Headache	186 (7)	180 (7)
	Urethritis	160 (6)	154 (6)
	Oropharyngeal pain	153 (6)	140 (5)
	Fatigue	147 (6)	163 (6)
	Gastroenteritis	145 (5)	115 (4)
	Pharyngitis	140 (5)	82 (3)

Source: Reviewer's analysis of ADAE dataset

Adverse Reactions

Adverse reactions (ARs) are defined as adverse events for which there is some basis to believe a causal relationship exists between the drug and the event (§ 201.57(c)(7)). Determination of a causal relationship is a matter of judgment but may be based on such factors as the frequency of reporting, whether the AE incidence rate for the drug exceeds the placebo rate, or the extent to which the AE is consistent with the pharmacology of the drug or is known to be caused by related drugs.

Study 2055 was not a placebo-controlled trial, but as both arms included similar drugs, the ARs (headache, abdominal pain, weight decrease) identified in the registrational, placebo-controlled trials of F/TDF for PrEP were reviewed. As previously noted, there were no significant between-group differences in Study 2055 with respect to the types or frequencies of most TEAEs. This was also true when the rates for the ARs reported in F/TDF labeling were compared: headache 7% each; abdominal pain (using the MedDRA HLT) F/TAF 5% vs. F/TDF 6%; weight decreased 1% each. As such, this reviewer concurred with the Applicant to define ARs as the subset of reported events deemed by the investigators to be study drug-related, recognizing that rate calculations based on the judgment of individual investigators may introduce bias and inconsistency in rate determinations.

Based on the above definition, ARs were reported in 20% and 23% of subjects in the F/TAF and F/TDF groups, respectively. In both groups, the most common ARs were GI-related. Again, there

were no notable differences between the groups with respect to the types or frequencies of ARs, although there was a slightly greater incidence of drug-related GI disorders in the F/TDF group (by MedDRA SOC: F/TAF 326 [12%], F/TDF 382 [14%]; risk difference 2%). Table 20 lists the ARs reported in at least 1% of subjects in either treatment group. In this table, events related to abdominal pain/discomfort were grouped together to yield a more precise estimate of clinically-related symptoms; product labeling for Descovy should follow suit.

Table 20: Treatment-Emergent Adverse Drug Reactions Reported in At Least 1% of Subjects in Either Treatment Group (GS-US-412-2055)

MedDRA High Level Term	*MedDRA Preferred Term*	*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)
	Total	545 (20)	629 (23)
	Diarrhea	135 (5)	160 (6)
	Nausea	114 (4)	123 (5)
	Fatigue	43 (2)	72 (3)
	Headache	59 (2)	57 (2)
	*Any abdominal pain**	63 (2)	88 (3)
Gastrointestinal and abdominal pains (excl oral and throat)		45 (2)	58 (2)
	Abdominal pain	26 (1)	35 (1)
	Abdominal pain upper	17 (1)	24 (1)
	Abdominal pain lower	1 (<1)	0
	Gastrointestinal pain	1 (<1)	0
Gastrointestinal signs and symptoms NEC	Abdominal discomfort	18 (1)	30 (1)
	Flatulence	22 (1)	32 (1)
	Abdominal distension	19 (1)	18 (1)
	Dizziness	16 (1)	24 (1)
	Vomiting	15 (1)	13 (1)
	Dyspepsia	11 (<1)	13 (1)
	Rash	13 (1)	9 (<1)
	Abnormal dreams	13 (1)	21 (1)
	Insomnia	11 (<1)	14 (1)
	Asthenia	10 (<1)	14 (1)

For this analysis, adverse reactions related to abdominal pain/discomfort were grouped together from the MedDRA High Level Terms 'Gastrointestinal and abdominal pains (excl oral and throat)' and 'Gastrointestinal signs and symptoms NEC'.
Source: Reviewer's analysis of ADAE dataset

8.4.6. Laboratory Findings

In Study 2055, there were no notable changes from baseline within groups or differences between groups in median values for hematology or clinical chemistry parameters, including liver-related laboratory tests.

There were no cases consistent with Hy's Law. This reviewer identified 13 subjects (F/TAF 10, F/TDF 3) with concurrent elevations in alanine aminotransferase (ALT) or aspartate

aminotransferase (AST) > 3 times the upper limit of normal (ULN) and total bilirubin > 2 times ULN, irrespective of alkaline phosphatase level. All 13 subjects had evidence of an infectious etiology for the elevations in their liver function tests, namely acute viral hepatitis and in one case, secondary syphilis.

The incidence of treatment-emergent, graded laboratory abnormalities was similar between the two groups for most parameters. Most laboratory abnormalities were Grade 1 or 2. Grade 2-4 laboratory abnormalities were reported in 26% and 27% of subjects in the F/TAF and F/TDF groups, respectively. The most common Grade 2-4 treatment-emergent laboratory abnormalities were: increased ALT (6% each arm), increased AST (6% each arm), fasting hyperglycemia (F/TAF 7%, F/TDF 8%), fasting hypercholesterolemia (F/TAF 9%, F/TDF 4%), and increased fasting low-density lipoprotein (LDL) (F/TAF 8%, F/TDF 5%).

Lipase was assessed in subjects with serum amylase > 1.5 times the ULN. The incidence of Grade 2-4 increased lipase was higher in the F/TDF group than in the F/TAF group: 43% vs. 32%, respectively; however, clinical pancreatitis was reported rarely (F/TAF 0, F/TDF 3 [0.1%]).

The frequencies of Grade 2-4 treatment-emergent laboratory abnormalities, using the maximum postbaseline toxicity grade for each parameter, are displayed in Table 21 for clinical chemistry parameters and in Table 22 for hematology parameters. Treatment-emergent fasting lipid abnormalities are discussed further in Section 8.5.4, and renal-associated laboratory parameters are discussed in Section 8.5.1.

Table 21: Treatment-Emergent Grade 2-4 Laboratory Abnormalities - Chemistry (GS-US-412-2055)

Laboratory Parameter		*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)
Alanine Aminotransferase (U/L)		N=2672	N=2664
	Grade 2	114 (4)	117 (4)
	Grade 3	21 (1)	24 (1)
	Grade 4	18 (1)	16 (1)
Aspartate Aminotransferase (U/L)		N=2672	N=2663
	Grade 2	101 (4)	118 (4)
	Grade 3	40 (2)	38 (1)
	Grade 4	23 (1)	13 (1)
Gamma Glutamyl Transferase (U/L)		N=2672	N=2665
	Grade 2	57 (2)	49 (2)
	Grade 3	15 (1)	7 (<1)
	Grade 4	3 (<1)	3 (<1)
Alkaline Phosphatase (U/L)		N=2672	N=2665
	Grade 2	7 (<1)	4 (<1)
	Grade 3	0	0
	Grade 4	1 (<1)	1 (<1)
Total Bilirubin (mg/dL)		N=2672	N=2665
	Grade 2	67 (3)	78 (3)
	Grade 3	8 (<1)	9 (<1)

	Grade 4	2 (<1)	1 (<1)
Amylase (U/L)		N=2672	N=2665
	Grade 2	57 (2)	70 (3)
	Grade 3	29 (1)	44 (2)
	Grade 4	5 (<1)	2 (<1)
Lipase (U/L)		N=117	N=133
	Grade 2	16 (14)	22 (17)
	Grade 3	18 (15)	29 (22)
	Grade 4	3 (3)	6 (5)
Uric acid (mg/dL) - *Hyperuricemia*		N=2762	N=2665
	Grade 2	42 (2)	30 (1)
	Grade 3	4 (<1)	3 (<1)
Fasting Glucose (mg/dL) - *Hyperglycemia*		N=2518	N=2515
	Grade 2	172 (7)	181 (7)
	Grade 3	11 (1)	17 (1)
	Grade 4	1 (<1)	0

Source: Reviewer's analysis of ADLB dataset

Table 22: Treatment-Emergent Grade 2-4 Laboratory Abnormalities - Hematology (GS-US-412-2055)

Laboratory Parameter		*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)
Hemoglobin (g/dL)		N=2761	N=2664
	Grade 2	17 (1)	6 (<1)
	Grade 3	7 (<1)	5 (<1)
	Grade 4	0	1 (<1)
Leukocytes (x10^3/uL)		N=2761	N=2664
	Grade 2	3 (<1)	4 (<1)
Lymphocytes (x10^3/uL)		N=2761	N=2664
	Grade 2	6 (<1)	8 (<1)
	Grade 3	2 (<1)	3 (<1)
Neutrophils (x10^3/uL)		N=2761	N=2664
	Grade 2	30 (1)	32 (1)
	Grade 3	14 (1)	7 (<1)
	Grade 4	6 (<1)	2 (<1)
Platelets (x10^3/uL)		N=2761	N=2664
	Grade 2	5 (<1)	7 (<1)
	Grade 3	2 (<1)	0

Source: Reviewer's analysis of ADLB dataset

8.4.7. Vital Signs

There were no clinically relevant changes from baseline in median values for all vital signs (blood pressure, heart rate, respiration rate, temperature) in either arm of Study 2055.

Body Weight

A growing body of literature has described an association between certain antiretroviral regimens and weight gain, in particular those containing integrase strand transfer inhibitors (INSTIs) {Norwood et al. 2017}. Recently, a retrospective cohort analysis reported a mean weight increase of 3.17% at 50 weeks in PLWH initiating a TAF-containing treatment regimen compared with a 0.55% increase in those initiating TDF-containing regimen {Gomez et al. 2019}.

In Study 2055, there was a mean (SD) weight increase of 1.1 (4.34) kg in the F/TAF group (n=2374) at Week 48 (corresponding to a 1.39% increase from baseline) and a mean (SD) decrease of -0.1 (4.4) kg in the F/TDF group (n=2369). A difference between groups was also noted in the proportion of subjects who experienced a ≥ 5% weight gain from baseline at Week 48: F/TAF 19% (454/2374) versus F/TDF 13% (302/2369).

At Week 96, the mean (SD) weight increase from baseline was 1.7 (5.49) kg in the F/TAF group (n=1109) and 0.6 (5.37) kg in the F/TDF group (n=1157). The proportion of subjects with ≥ 5% weight gain from baseline at Week 96 remained greater for the F/TAF group: F/TAF 30% (329/1109) versus F/TDF 20% (234/1157).

There were no notable differences between the groups in the proportion of subjects with TEAES related to weight changes or appetite (Table 23).

Table 23: Treatment-Emergent Adverse Events Related to Weight Change (GS-US-412-2055)

MedDRA System Organ Class	*MedDRA Preferred Term*	*Number (%) of Subjects*	
		F/TAF N=2694	F/TDF N=2693
Investigations	Weight increased	28 (1)	16 (1)
	Weight decreased	25 (1)	33 (1)
Metabolism and nutrition disorders	Abnormal weight gain	3 (<1)	0
	Abnormal loss of weight	8 (<1)	7 (<1)
	Increased appetite	5 (<1)	3 (<1)
	Decreased appetite	19 (1)	23 (1)
	Metabolic syndrome	1 (<1)	0

Source: Reviewer's analysis of ADAE dataset

> *<u>Reviewer comment</u>: As noted above, a mean increase in body weight of 1.1 kg from baseline was observed in the F/TAF group at Week 48, whilst no change was seen in the F/TDF group. Similar weight increases were reported in the placebo group of the iPrEx trial (versus transient decreases in the F/TDF group) and increases of around 1 kg per year are reportedly typical in the average American aged 20 to 40 years {Glidden et al. 2018; Hill et al. 2003}. Taken together, these findings might suggest that rather than F/TAF directly causing weight gain, F/TDF may have a modest suppressive effect on*

expected weight gain (independent of treatment-emergent nausea) in an HIV-uninfected population, which may explain the between-group differences observed here.

8.4.8. Electrocardiograms (ECGs)

Electrocardiograms (ECGs) were not routinely collected during Study 2055. Three subjects had TEAEs related to abnormal ECGs: two subjects with electrogram abnormal (1 subject in each arm) and one subject with QRS axis abnormal in the F/TAF group. All three subjects were > 50 years of age, and two of the events occurred in the context of concurrent SAEs (i.e., pneumonia and sepsis). None of the ECG events was considered related to study drug by the investigators.

8.4.9. QT

A previously conducted thorough QT study with TAF did not demonstrate any effect on the QT/QTc or PR intervals (refer to the Descovy USPI). The effect of FTC, or the combination of FTC and TAF, on the QT interval is not known.

8.4.10. Immunogenicity

As FTC and TAF are small molecules, immunogenicity issues are not anticipated and were not specifically addressed during Study 2055.

8.5. Analysis of Submission-Specific Safety Issues

Based on available preclinical and clinical data, the following potential safety issues have been identified for F/TAF and warranted further evaluation in this application: renal safety (in particular, development of proximal renal tubulopathy), BMD changes, and changes in fasting serum lipid levels. Weight increase is another potential signal that has been reported in the postmarket setting and was discussed in Section 8.4.7.

<u>Reviewer comment:</u> Other potential safety concerns raised during the original NDA review of TAF (as part of Genvoya, NDA 207561), such as uveitis or dental disorders, were not borne out by further assessments, including subsequent clinical trials of TAF monotherapy for an HBV indication (see original review of NDA 208464 for Vemlidy), and are therefore not reviewed in detail this application. Suffice to say, no differences were observed in Study 2055 between the F/TAF and F/TDF groups with respect to dental or ocular disorders for terms across the MedDRA hierarchy.

8.5.1. Renal Safety

Tenofovir disoproxil fumarate has been associated with an increased risk of renal adverse events, including proximal renal tubulopathy (e.g., Fanconi syndrome) and acute renal failure.

The risk of nephrotoxicity is believed to be related to circulating TFV plasma levels. Reduced systemic TFV exposures with TAF administration, therefore, are hypothesized to result in fewer renal adverse events. Indeed, previous clinical trials of TAF for the treatment of HIV-1 or HBV have demonstrated an improved renal safety profile compared with TDF as determined by various laboratory biomarkers of renal tubular function. In Study 2055, renal safety was reviewed to assess whether this differential extended to HIV-uninfected individuals as well.

Treatment-Emergent Renal Adverse Events

For the analysis of renal-associated TEAEs, this reviewer selected MedDRA PTs from twelve HLTs in the 'Renal and urinary disorders' and 'Investigations' SOCs (obstructive disorders, neoplasms, vascular and ischemic events, and lithiasis events were excluded). By this method, renal-associated events were reported in 176 (3%) subjects overall (F/TAF 79 [3%], F/TDF 97 [4%]). Table 24 lists all the TEAEs by MedDRA HLT and PT. (Note: certain PTs not considered related to renal function are not displayed in the table.)

Table 24: Selected Renal-Associated Treatment-Emergent Adverse Events (GS-US-412-2055)

MedDRA System Organ Class	*MedDRA High Level Term*	*MedDRA Preferred Term*	*Number (%) of Subjects*	
			F/TAF (N=2694)	F/TDF (N=2693)
		Total	79 (3)	97 (4)
Renal and urinary disorders	*Glomerulonephritis and nephrotic syndrome*	Nephrotic syndrome	1 (<1)	0
	Nephropathies and tubular disorders NEC		1 (<1)	1 (<1)
		Fanconi syndrome acquired	0	1 (<1)
		Glomerulonephropathy	1 (<1)	0
	Renal failure and impairment		13 (1)	19 (1)
		Acute kidney injury	13 (1)	7 (<1)
		Chronic kidney disease	0	5 (<1)
		Prerenal failure	0	1 (<1)
		Renal failure	0	1 (<1)
		Renal impairment	0	7 (<1)
	Urinary abnormalities		64 (2)	65 (2)
		Glycosuria	4 (<1)	8 (<1)
		Microalbuminuria	0	3 (<1)
		Proteinuria	30 (1)	32 (1)
		Urine abnormality	4 (<1)	0
	Urinary tract signs and symptoms NEC		16 (1)	19 (1)
		Nocturia	7 (<1)	5 (<1)
		Polyuria	1 (<1)	4 (<1)
Investigations	*Mineral and electrolyte analyses*	Blood phosphorus decreased	3 (<1)	1 (<1)
	Renal function analyses		15 (1)	34 (1)
		Blood creatinine decreased	1 (<1)	0
		Blood creatinine increased*	7 (<1)	16 (1)

		Creatinine renal clearance decreased	3 (<1)	5 (<1)
		Creatinine renal clearance increased	0	3 (<1)
		Glomerular filtration rate abnormal	1 (<1)	0
		Glomerular filtration rate decreased	1 (<1)	4 (<1)
		Urine albumin/creatinine ratio increased	1 (<1)	0
		Urine protein/creatinine ratio increased	2 (<1)	8 (<1)
	Urinalysis NEC		8 (<1)	7 (<1)
		Protein urine present	3 (<1)	1 (<1)
		Urine analysis abnormal	2 (<1)	0

*'Blood creatinine increased' includes one subject (Subject (b) (6)) in the F/TDF arm with a TEAE coded as 'blood *creatine* increased'. Review of the subject's laboratory data revealed increasing serum creatinine around the time the event was recorded; therefore, the TEAE was reassigned as 'blood creatinine increased'.
Source: Reviewer's analysis of ADAE dataset

As shown in Table 24, there was essentially no difference between the treatment groups with respect to the incidence or types of renal-associated TEAEs, whether by MedDRA HLT or PT. Most (74%) of these TEAEs were Grade 1. Moderate to severe (Grade 2-3) TEAEs were reported in 1% of subjects in each arm, with comparable rates of specific TEAEs by MedDRA PT; there were no Grade 4 events. Likewise, no differences were observed when rates of MedDRA SMQs for acute renal failure (broad and narrow) were compared (risk differences < 0.5 per hundred).

Renal-associated SAEs were reported in 8 subjects (F/TAF 6 [0.2%], F/TDF 2 [0.1%]). The SAEs included acute kidney injury (F/TAF 5 [0.2%], F/TDF 2 [0.1%]) and nephrotic syndrome (F/TAF 1 [0.04%]). The median time to onset was 533 days (range 41-647 days). Only the event of nephrotic syndrome and one of the events of acute kidney injury in the F/TAF group were considered related to study drug by the investigators, whereas both events of acute kidney injury in the F/TDF group were considered drug-related. Renal-associated SAEs are reviewed in more detail in Table 26.

Importantly, a small but similar proportion of subjects in each arm discontinued study drug due to a renal-associated TEAE (F/TAF 5 [0.2%], F/TDF 8 [0.3%]), as shown in Table 25. Likewise, an equal proportion (0.2%) of subjects in each arm interrupted study drug due to a renal event. For the latter, TEAEs reported in at least two subjects included: acute kidney injury (F/TAF 4 [0.2%], F/TDF 1 [0.04%]) and renal impairment (F/TAF 0, F/TDF 2 [0.1%]). These cases are also explored further in Table 26.

Table 25: Renal-Associated Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal (GS-US-412-2055)

MedDRA Preferred Term	*Number (%) of Subjects*	
	F/TAF (N=2694)	F/TDF (N=2693)
Total	5 (0.2)	8 (0.3)
Acute kidney injury	2 (0.1)	2 (0.1)
Fanconi syndrome acquired	0	1 (<0.1)
Proteinuria	0	1 (<0.1)
Renal impairment	0	2 (0.1)
Blood creatinine increased	3 (0.1)	1 (<0.1)
Glomerular filtration rate decreased	0	1 (<0.1)

Source: Reviewer's analysis of ADAE dataset

Potential cases of proximal renal tubulopathy (PRT) were reviewed. The Applicant identified subjects with PRT utilizing investigator-reported events for the following MedDRA PTs: Fanconi syndrome, Fanconi syndrome acquired, renal tubular disorder, renal tubular dysfunction, and renal tubular injury. By this method, one subject (Subject [redacted]) in the F/TDF group was identified with Fanconi syndrome acquired; his narrative is as follows:

- Subject [redacted] (F/TDF): This 49-year-old man (U.S.) was reported to have Grade 3 nonserious Fanconi syndrome acquired on Study Day 421 (Week 60). The event was marked by graded laboratory abnormalities of low serum phosphate, high serum creatinine, low $eGFR_{CG}$, high urine glucose, high urine protein, and elevated urine β2M to creatinine ration, urine RBP to creatinine ratio, and UPCR. No relevant medical history was reported, and there were no other relevant TEAEs around the time of the event. His estimated adherence rate to study drug was 73%; he had not been on Truvada for PrEP prior to study. The event was considered related to study drug by the investigator and drug was discontinued. The event was considered resolved on Study Day 435, when serum creatinine and $eGFR_{CG}$ improved; however, renal indices had not fully recovered to baseline values as of Study Day 589.

FDA reviewers further explored the Study 2055 laboratory dataset to identify other potential cases of PRT employing criteria previously used in the NDA reviews of other tenofovir-containing products (NDA 203100 for Stribild and NDA 207561 for Genvoya) and the CYP3A inhibitor cobicistat (NDA 203094 Tybost). For this analysis, potential PRT was defined as confirmed laboratory abnormalities in any two of the following four parameters (serum creatinine and three markers of tubular dysfunction):

- Increase in serum creatinine ≥ 0.24 mg/dL from baseline
- ≥ 2 grade level increase from baseline in proteinuria
- ≥ 1 grade level increase from baseline in hypophosphatemia

- ≥ 1 grade level increase from baseline in glycosuria concurrent with serum glucose ≤ 100 mg/dL (normoglycemic glycosuria)

A confirmed laboratory abnormality was defined as that observed at two consecutive post-baseline measurements or at one measurement followed by study drug discontinuation.

In this analysis, one potential case of PRT was identified in the F/TAF arm. The subject's narrative is as follows:

- Subject (b) (6) (F/TAF): This 36-year-old, African-American man (U.S.) experienced non-serious, Grade 2 acute kidney injury on Study Day 333 (Week 48). The event was marked by high serum creatinine (baseline = 1.25 mg/dL; Week 48 = 2.02 mg/dL), high urine protein, a decrease in $eGFR_{CG}$ of 45 mL/min from baseline, and elevated β2M and RBP to creatinine ratios and UPCR. His medical history was relevant for hypertension; no other TEAEs were reported around the time of the event. His estimated adherence rate to study drug was 89%, and he had been taking Truvada for PrEP at baseline. The event was considered related to study drug by the investigator and drug was discontinued; however, the event remained unresolved as of the data cut-off date (serum creatinine = 2.2 mg/dL, with near-nephrotic range proteinuria [3.4 g/day]).

  Follow-up provided by the Applicant during this review indicated that the subject's serum creatinine continued to increase for many months off F/TAF, ranging between 2.5 to 3.1 mg/dL. Nine months after the last dose of F/TAF, a renal biopsy was performed, and findings included moderate arterionephrosclerosis and focal and segmental glomerulosclerosis (FSGS). The subject was placed on systemic steroid therapy and his serum creatine improved modestly, with a nadir of 2.5 mg/dL as of May 2019.

Reviewer comment: While the above case met 2 out of the 4 nonspecific screening criteria for possible PRT, there was no evidence of normoglycemic glycosuria, phosphate wasting, or metabolic acidosis, which have been reported as manifestations of renal toxicity with TDF. The elevations in serum creatinine and near-nephrotic range proteinuria are explained by hypertensive nephropathy and FSGS as determined by renal biopsy. Further, the pattern of proteinuria in this case is distinct from that observed with PRT. In PRT, β2M and RBP to creatinine ratios increase dramatically while total urine protein (UPCR) is minimally elevated, demonstrating a specific defect in proximal tubular function. Conversely, in this case, total proteinuria was markedly elevated and the modest elevations in β2M and RBP to creatinine ratios were likely due to gross spillage of protein as a result of glomerular injury.

Table 26 summarizes the 16 subjects who experienced adverse events of renal failure or nephropathies that were serious and/or led to study drug discontinuation or interruption.

Table 26: Treatment-Emergent Renal Adverse Events - Serious or Leading to Drug Interruption or Withdrawal (GS-US-215-2055)

Arm	Subject	Age	MedDRA PT	Onset Day	SAE	Grade	Action with Study Drug	Related to Study Drug		Outcome	FDA Comment
								Investigator	FDA		
F/TAF	(b) (6)	19	Acute kidney injury	459	Yes	3	Drug Interrupted	No	No	Resolved Day 478	Concurrent scrotal abscess/sepsis treated with intravenous antibiotics
		53	Glomerulonephropathy	468	No	2	Drug Interrupted	No	Unlikely	Ongoing	Podocytic infolding glomerulopathy – treated with prednisone
		31	Nephrotic syndrome	279	Yes	3	Drug interrupted	Yes	Possibly	Resolved Day 282	Likely multifactorial. Recent history of syphilis and rectal/pharyngeal gonorrhea
		22	Acute kidney injury	615	Yes	3	Drug Interrupted	No	No	Ongoing	Heroin overdose, rhabdomyolysis, aspiration pneumonia
		21	Acute kidney injury	635	Yes	2	None	No	No	Resolved Day 640	Concurrent serious Campylobacter/E. coli gastroenteritis
		44	Acute kidney injury	159	No	1	Drug Withdrawn	No	No	Resolved Day 160	Concurrent myocardial infarction, history of hypertension
		58	Acute kidney injury	149	Yes	2	Drug Interrupted	No	No	Resolved Day 151	Concurrent supraventricular tachycardia; renal indices not changed
		69	Acute kidney injury	41	Yes	3	Drug Interrupted	No	No	Resolved Day 43	Concurrent shigella gastroenteritis
		36	Acute kidney injury	333	No	2	Drug Withdrawn	Yes	Yes	Ongoing	Baseline eGFR 132 mL/min decreased to 87.3 mL/min on Day 333; (+) proteinuria; on Truvada for PrEP at baseline
F/TDF		42	Renal impairment	445	No	1	Drug Withdrawn	Yes	Unlikely	Ongoing	Concurrent syphilis. Baseline serum creatinine high (1.57 mg/dL) and eGFR low (72.7 mL/min) at screening.
		49	Fanconi syndrome acquired	421	No	3	Drug Withdrawn	Yes	Yes	Resolved Day 435	Renal labs consistent with Fanconi syndrome; no alternative etiology noted
		44	Acute kidney injury	170	No	2	Drug Withdrawn	Yes	Possibly	Ongoing	Baseline serum creatinine high (1.25 mg/dL) and eGFR low (72.7 mL/min); worsened on study drug, but not improved with discontinuation and worse at Day 590
		64	Acute kidney injury	647	Yes	2	Drug Withdrawn	Yes	Possibly	Ongoing	Hospitalized for hip pain, on multiple NSAIDs. Baseline serum creatinine 1.48 mg/dL. Hypertensive nephropathy
		52	Acute kidney injury	607	Yes	3	Drug Interrupted	Yes	No	Resolved Day 616	Concurrent influenza pneumonia with dehydration
		53	Renal impairment	674	No	2	Drug Interrupted	Yes	Possibly	Ongoing	Modest decline in serum creatinine and eGFR
		63	Renal impairment	249	No	2	Drug Withdrawn	Yes	Possibly	Ongoing	Likely multifactorial. Baseline eGFR low (64.3 mL/min) and <60 mL/min during study. Multiple NSAIDs for migraine headaches

eGFR = estimated glomerular filtration rate; MRI = magnetic resonance imagining; NSAID = nonsteroidal anti-inflammatory drug
Source: Reviewer's analysis of ADAE datasets, subject narratives

Renal Laboratory Findings

Serum Creatinine and Creatinine Clearance

Table 27 displays the mean change from baseline in serum creatinine by study week. As shown, there was minimal change in serum creatinine in either treatment group through Week 96.

Table 27: Mean Change from Baseline in Serum Creatinine (GS-US-412-2055)

Study Visit	F/TAF (N=2694)			F/TDF (N=2693)		
	N	Mean Change (mg/dL)	Std Dev	N	Mean Change (mg/dL)	Std Dev
Baseline	2694	0.96 mg/dL	0.146	2693	0.96 mg/dL	0.148
Week 4	2658	0.00	0.104	2651	0.02	0.105
Week 12	2582	0.00	0.108	2582	0.02	0.108
Week 24	2481	0.00	0.105	2484	0.01	0.104
Week 36	2407	-0.01	0.109	2415	0.01	0.110
Week 48	2371	-0.01	0.106	2369	0.01	0.110
Week 60	2327	0.00	0.112	2329	0.03	0.117
Week 72	2264	0.01	0.111	2282	0.03	0.115
Week 84	2211	0.01	0.113	2237	0.03	0.118
Week 96	1210	0.01	0.115	1264	0.02	0.116

Source: Reviewer's analysis of ADLB dataset

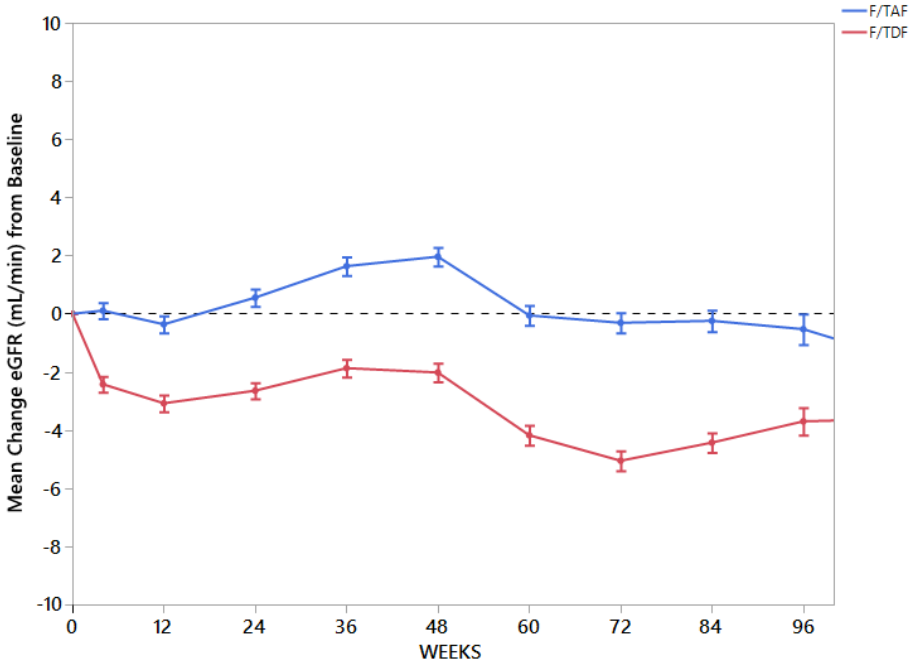
Table 28 displays the corresponding changes in creatinine clearance at each study week. There was minimal change from baseline in $eGFR_{CG}$ through Week 96 in the F/TAF group, whereas there was a mean 2-5 mL/min decrease in the F/TDF group (Figure 7).

Table 28: Mean Change from Baseline in Estimated Glomerular Filtration Rate (Cockcroft-Gault) (GS-US-412-2055)

Study Visit	F/TAF (N=2694)			F/TDF (N=2693)		
	N	Mean Change (mL/min)	Std Dev	N	Mean Change (mL/min)	Std Dev
Baseline	2694	127.9 mL/min	34.30	2693	126.4 mL/min	34.30
Week 4	2654	0.2	14.23	2649	-2.4	13.97
Week 12	2579	-0.4	14.64	2582	-3.0	14.76
Week 24	2478	0.6	14.74	2483	-2.6	13.95
Week 36	2403	1.7	15.72	2414	-1.9	15.11
Week 48	2370	2.0	15.84	2367	-2.0	15.77
Week 60	2326	-0.1	16.51	2327	-4.1	16.30
Week 72	2263	-0.3	16.67	2281	-5.0	16.30
Week 84	2210	-0.2	17.18	2237	-4.4	16.05
Week 96	1208	-0.6	18.25	1262	-3.7	16.90

Source: Reviewer's analysis of ADLB dataset

Figure 7: Mean Change in Estimate Glomerular Filtration Rate by Cockcroft-Gault (mL/min) from Baseline (GS-US-412-2055)



Source: Reviewer's analysis of ADLB dataset

Urinary Biomarkers of Proximal Renal Tubulopathy

Beta-2-microglobulin is a low molecular weight protein produced by all cells expressing major histocompatibility complex class I antigen. It is readily filtered through the glomerulus and almost completely reabsorbed by the proximal tubules. When proximal tubule cells are damaged, an increase in excretion of urinary β2M results from impaired reabsorption in the proximal tubule, making urinary β2M a reliable biomarker of renal tubulopathy {Miyata et al. 1998}.

Similarly, RBP is another low molecular weight protein, whose main function is to transport retinol (vitamin A). About 4-5% of serum RBP-retinol circulates freely, passes the glomerular barrier and is then reabsorbed and degraded in the proximal tubule. Urinary RBP as a biomarker of proximal tubular dysfunction is often used as a diagnostic tool in proximal tubulopathies, such as Fanconi syndrome {Domingos et al. 2016}.

Percentage changes from baseline in urine β2M and urine RBP to creatinine ratios at Week 48 (using observed on-treatment data) were two of the six key alpha-controlled secondary endpoints for Study 2055. As shown in Table 29 and Table 30, there were minimal changes or decreases from baseline in the F/TAF group for both parameters, compared with increases in

the F/TDF group. Per the Applicant, the differences between the treatment groups were statistically significant at all time points from Week 4 to Week 96.

Table 29: Median Percentage Change from Baseline in Urine **β2-Microglobulin** to Creatinine Ratio (GS-US-412-2055)

Study Visit	F/TAF (N=2694)			F/TDF (N=2693)		
	N	Median % Change	Q1, Q3	N	Median % Change	Q1, Q3
Baseline	2677	84.2 ug/g	60.5, 131.6	2676	85.6 ug/g	63.1, 134.1
Week 4	2614	-6.3%	-35.0, 30.9	2618	+10.3%	-22.6. 71.7
Week 48	2346	-10.7%	-42.0, 25.9	2337	+15.4%	-22.9, 97.4
Week 96	1181	-17.2%	-47.8, 19.2	1232	+11.0%	-26.9, 88.7

Source: Reviewer's analysis of ADLB dataset

Table 30: Median Percentage Change from Baseline in Urine Retinol Binding Protein to Creatinine Ratio (GS-US-412-2055)

Study Visit	F/TAF (N=2694)			F/TDF (N=2693)		
	N	Median % Change	Q1, Q3	N	Median % Change	Q1, Q3
Baseline	2686	100.9 ug/g	73.2, 140.6	2686	103.7 ug/g	75.4, 146.4
Week 4	2646	-2.2%	-25.4, 28.9	2641	+8.3%	-19.5, 46.5
Week 48	2360	+0.1%	-24.9, 35.5	2354	+20%	-12.8, 68.2
Week 96	1204	-2.1%	-31.0, 33.4	1259	+19.9%	-16.1, 73.2

Source: Reviewer's analysis of ADLB dataset

> *<u>Reviewer comment</u>: While β2M and RBP to creatinine ratios are increasingly being used in investigational studies as biomarkers of proximal renal tubulopathy, they have not undergone formal qualification and their use remains exploratory for regulatory purposes. These tests are not commonly used in routine clinical practice, and the long-term clinical significance of changes in these biomarkers remains unclear.*

Urine protein to creatinine ratio (UPCR) is generally regarded by the FDA Division of Cardiovascular and Renal Products as a useful laboratory assessment of proteinuria. The median baseline UPCR among subjects who had nonmissing values at both baseline and Week 48 (F/TAF n=2390, F/TDF n=2382) was 35 mg/g and 37 mg/g for F/TAF and F/TDF, respectively; at Week 48, these values were 35 mg/g and 38 mg/g, respectively. The majority of subjects had UPCR ≤ 200 mg/g at baseline and during the trial.

The distribution of urine protein and UPCR categories ≤ 200 mg/g versus > 200 mg/g at Week 48 was another key alpha-controlled safety endpoint for this trial. As shown in Table 31, a smaller proportion of subjects in the F/TAF group had worsening of UPCR category at Week 48 compared with the F/TDF group (1% vs. 2%, respectively). Conversely, a greater proportion of subjects in the F/TAF group had improvement in UPCR category from baseline compared with

the F/TDF group at both Weeks 48 and 96; however, the number of subjects with UPCR > 200 mg/g at baseline was small (n=25 per arm). Further, the differences between the treatment groups were only statistically significant at Week 48, but not at Week 96.

Table 31: Shift Table of Urine Protein to Creatinine Ratio Category **(≤200** vs. >200 mg/g) by Baseline Category (GS-US-412-2055)

	F/TAF (N=2694)		F/TDF (N=2693)	
	Baseline		*Baseline*	
	≤200 mg/g (N=2662)	>200 mg/g* (N=25)	≤200 mg/g (N=2657)	>200 mg/g* (N=25)
Week 48	*Number (%) of Subjects*		*Number (%) of Subjects*	
≤200 mg/g	2319 (99)	12 (57)	2296 (98)	8 (44)
>200 mg/g*	16 (1)	9 (43)	35 (2)	10 (56)
Week 96	*Number (%) of Subjects*		*Number (%) of Subjects*	
≤200 mg/g	1157(99)	10 (71)	1213 (99)	4 (36)
>200 mg/g*	15 (1)	4 (29)	15 (1)	7 (64)

* Includes subjects with UPCR >200 mg/g and UP ≥4 mg/dL.
Only subjects with nonmissing baseline UPCR values included. The denominator for percentages is the column total (i.e., subjects with nonmissing values at both baseline and at each postbaseline visit).
Source: Reviewer's analysis of ADLB dataset

Graded Renal Laboratory Abnormalities

Table 32 lists selected renal laboratory abnormalities, using the maximum postbaseline severity for each laboratory parameter. Most renal-associated laboratory abnormalities were Grade 1 and in general, the frequencies of abnormal laboratory tests were comparable between the two treatment groups. Although twice as many subjects in the F/TDF group as in the F/TAF group experienced graded elevations in serum creatinine, the percentages were low (2% vs. 1%, respectively). Likewise, the proportion of subjects with graded proteinuria by urine dipstick was higher in the F/TDF group than in F/TAF group (24% vs. 21%, respectively). The vast majority of these abnormalities, however, were Grade 1 (1+ by urine dipstick) and transient; the frequency of Grade 2 proteinuria (2-3+) was the same in both treatment groups at 2%.

Table 32: Treatment-Emergent Laboratory Abnormalities - Renal (GS-US-412-2055)

Laboratory Parameter		*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)
Creatinine (mg/dL)		N=2672	N=2665
	Grade 1	23 (1)	61 (2)
	Grade 2	5 (<1)	3 (<1)
Blood Urea Nitrogen (mg/dL)		N=2672	N=2665
	Grade 1	58 (2)	44 (2)
Phosphate (mg/dL) – Hypophosphatemia		N=2672	N=2665

	Grade 1	144 (5)	143 (5)
	Grade 2	87 (3)	76 (3)
	Grade 3	6 (<1)	5 (<1)
	Grade 4	0	2 (<1)
Magnesium (mg/dL) - Hypomagnesemia		N=2672	N=2665
	Grade 1	14 (1)	7 (<1)
	Grade 2	5 (<1)	3 (<1)
	Grade 3	2 (<1)	1 (<1)
	Grade 4	4 (<1)	0
Urine Protein		N=2671	N=2662
	Grade 1	518 (19)	592 (22)
	Grade 2	50 (2)	55 (2)
Urine Glucose		N=2671	N=2662
	Grade 1	15 (1)	23 (1)
	Grade 2	22 (1)	30 (1)
	Grade 3	19 (1)	32 (1)

Source: Reviewer's analysis of ADLB dataset

Summary of Renal Safety

Results from Study 2055 indicate that use of F/TAF as PrEP has favorable effects on urinary biomarkers of renal tubular function relative to F/TDF at 48 weeks. The short-term clinical benefit of these differences, however, is less evident as the incidence of renal-associated TEAEs, SAEs, or events leading to drug discontinuation, as well as the frequency of graded renal laboratory abnormalities, were generally comparable between the two treatment groups. Of note, approved U.S. labeling for Descovy still carries a Warning and Precaution (5.3) related to new or worsening renal impairment.

8.5.2. Bone Safety

Bone Treatment-Emergent Adverse Events

The Applicant identified PTs for fracture events based on the SMQ of osteoporosis/osteopenia and MedDRA HLGT of fractures. Accordingly, fracture events were reported in 53 (2%) subjects in each treatment group. Of the 116 fracture events reported, 91% were related to trauma. Ten subjects (5 per arm) had non-traumatic fractures, of which two (1 per arm) had right foot stress fractures and three (F/TAF 1, F/TDF 2) had pathological fractures as determined by blinded medical monitor assessment.

> *Reviewer comment: The list of MedDRA PTs used by the Applicant to identify fracture events was deemed acceptable by this reviewer.*

The three pathological fracture cases are reviewed below. None of the events was considered related to study drug by the investigators and study drug was continued in each case. Also, none of the three subjects participated in the DXA substudy.

- Subject (b) (6) (F/TDF): This 72-year-old man (U.S.) experienced a nonserious, Grade 2, non-traumatic fracture of the left shoulder on Study Day 404. Past medical history was significant for Type II diabetes mellitus. The event was preceded by worsening of serum creatinine and $eGFR_{CG}$ and development of proteinuria.

- Subject (b) (6) (F/TDF): This 52-year-old man (Canada) experienced a nonserious, Grade 1, non-traumatic fracture of the right 4th metatarsal on Study Day 497. Relevant information includes concomitant use of anabolic steroids for bodybuilding, past medical history of Hashimoto's thyroiditis, and a TEAE of hypophosphatemia on Study Day 28. He was treated with phosphoric acid sodium for the hypophosphatemia, and calcium and Vitamin D for prevention of osteoporosis. There were no other renal-associated TEAEs or confirmed changes in renal biomarkers.

- Subject (b) (6) (F/TAF): This 65-year-old man (U.S.) experienced a nonserious Grade 1, nontraumatic, vertebral fracture of the cervical spine on Study Day 404. Past medical history was significant for Sjogren's syndrome, degenerative disc disease (including cervical disc disease), and arthritis. There were no renal-associated TEAEs or notable changes in renal biomarkers.

  Reviewer comments: In each of the above cases, a pathological fracture could not be ruled out. Whether any of these fractures was related to tenofovir use could not be determined as there were confounding factors in each case that may have contributed to the event.

  In addition, the seven remaining cases of nontraumatic fractures were reviewed and no findings were observed to suggest a pathological condition or drug-related event. In contrast to the above, these seven cases occurred in a younger cohort (median age 36 years) and all involved distal extremity fractures, raising the question of whether they were truly nontraumatic.

Table 33 summarizes the fracture events reported in Study 2055. The table also includes other AEs related to nonspecific pain, as some of these can be associated with osteomalacia in adults {Gifre et al. 2011}. Also included are MedDRA PTs related to bone mineral density, osteopenia, and osteoporosis, as well as the SMQs for the latter two conditions.

As shown in the table, there were no differences between the two groups in the incidence of any of these events. All TEAEs of bone density decreased, bone loss, osteopenia and

osteoporosis were Grade 1 or 2 severity. Study drug was discontinued in four subjects due to bone-related adverse events, two (0.07%) for osteoporosis in the F/TAF group and two for back pain (1 [0.03%] per arm).

Table 33: Treatment-Emergent Adverse Events Related to Bone Safety (GS-US-412-2055)

	MedDRA Preferred Term	*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)
All fractures		53 (2)	53 (2)
Non-traumatic fractures		5 (<1)	5 (<1)
Non-traumatic stress fractures		1 (<1)	1 (<1)
Non-traumatic pathological fractures		1 (<1)	2 (<1)
	Back pain	98 (4)	103 (4)
	Pain in extremity	44 (2)	32 (2)
	Limb discomfort	1 (<1)	2 (<1)
	Bone pain	2 (<1)	3 (<1)
	Flank pain	5 (<1)	6 (<1)
	Spinal pain	4 (<1)	8 (<1)
	Coccydynia	1 (<1)	0
	Bone density decreased	5 (<1)	1 (<1)
	Bone loss	1 (<1)	1 (<1)
	Osteopenia	12 (<1)	15 (1)
	Osteoporosis	5 (<1)	7 (<1)
	Vitamin D deficiency	24 (1)	18 (1)
	Vitamin D decreased	4 (<1)	2 (<1)
	Blood phosphorus decreased	3 (<1)	1 (<1)
	Hypocalcemia	1 (<1)	0
SMQ osteoporosis/osteopenia (broad)		34 (1)	37 (1)
SMQ osteoporosis/osteopenia (narrow)		23 (1)	22 (1)

Source: Reviewer's analysis of ADAE dataset

Bone Mineral Density Substudy

The Hip and Spine DXA Analysis Sets included all participants in the Safety Analysis Set with nonmissing baseline hip or spine BMD values. As such, the DXA substudy safety population consisted of 383 subjects (F/TAF 194, F/TDF 189). The median (Q1, Q3) age of subjects in the substudy was 37 (29, 46) years; 10% were less than 25 years of age. The majority of subjects were white (86%) and MSM (99%). Median (Q1,Q3) exposures to study drug were 96.1 (84.1, 108.8) weeks in the F/TAF group and 96.4 (84.1, 109.3) weeks in the F/TDF group.

Changes in BMD from Baseline

The percentage changes from baseline in BMD at the hip and spine at Week 48 (observed data)

were key alpha-protected safety endpoints for Study 2055. As shown in Table 34, mean increases from baseline to Week 48 of 0.2% at the total hip and 0.5% at the lumbar spine were observed in the F/TAF group, compared to mean decreases of 1.0% at the total hip and 1.1% at the lumbar spine in the F/TDF group. Similar trends were observed at Week 96. Per the Applicant, the differences between the treatment groups were statistically significant at both Weeks 48 and 96.

Table 34: Mean Percentage Change from Baseline in Hip and Spine BMD (GS-US-412-2055)

	F/TAF	F/TDF
Hip BMD[1]		
Baseline	N=190	N=185
Mean (SD) (g/ cm^2)	1.029 (0.154)	1.02 (0.132)
Week 48	N=158	N=158
Mean (SD) % Change from Baseline	+0.2% (2.384)	-1.0 % (2.435)
Week 96	N=100	N=105
Mean (SD) % Change from Baseline	+0.4% (2.612)	-1.2% (2.897)
Spine BMD[2]		
Baseline	N=190	N=188
Mean (SD) (g/cm^2)	1.131 (0.161)	1.131 (0.138)
Week 48	N=159	N=160
Mean (SD) % Change from Baseline	+0.5% (2.988)	-1.1% (2.945)
Week 96	N=100	N=112
Mean (SD) % Change from Baseline	+0.9% (3.143)	-1.3% (3.918)

[1] Hip BMD = Femur Total Corrected Bone Mineral Density (g/cm2)
[2] Spine BMD = Spine Total Adequate Corrected Bone Mineral Density (g/cm2)
Source: Reviewer's analysis of ADDXA dataset

Categorical BMD Analyses

Overall, a higher percentage of subjects in the F/TDF group experienced a decrease from baseline BMD, of any magnitude, at both anatomical sites, whether at Week 48 or Week 96. The Applicant conducted a categorical analysis of percentage change from baseline in hip and spine BMD using a ≥ 3% change from baseline as a cut-off. As shown in Table 35, a greater proportion of subjects in the F/TDF arm compared to the F/TAF arm had a ≥ 3% decrease from baseline in hip and spine BMD at both Weeks 48 and 96; per the Applicant, these differences were statistically significant at both time points. Conversely, a greater proportion of subjects in the F/TAF arm had a ≥ 3% increase from baseline BMD at both anatomical sites at both time points; however, the between-group differences were not significant.

The FDA, on the other hand, considers a ≥ 7% change from baseline BMD at the hip region and a ≥ 5% change from baseline BMD at the spine region to be more clinically meaningful. These cut-offs were also recommended in the protocol for Study 2055 for investigators to use in the management of subjects with BMD decreases. Using these cut-offs, the differences between

the treatment groups were not statistically significant at Week 48, and only the difference at Week 96 in the proportion of subjects with ≥ 5% decrease from baseline spine BMD was significant (Table 35).

Table 35: Categorical Distribution of Percentage Changes in Hip and Spine BMD (GS-US-412-2055)

	Number (%) of Subjects	
	F/TAF	F/TDF
Hip BMD	N=190	N=185
Week 48		
No Decrease from Baseline	79/158 (50)	54/158 (34)
≥ 3% Decrease from Baseline	6/158 (4)	29/158 (18)
≥ 7% Decrease from Baseline	2/158 (1)	2/158 (1)
≥ 3% Increase from Baseline	14/158 (9)	10/158 (6)
≥ 7% Increase from Baseline	1/158 (1)	1/158 (1)
Week 96		
No Decrease from Baseline	57/100 (57)	40/105 (38)
≥ 3% Decrease from Baseline	5/100 (5)	22/105 (21)
≥ 7% Decrease from Baseline	0	2/105 (2)
≥ 3% Increase from Baseline	12/100 (12)	4/105 (4)
≥ 7% Increase from Baseline	1/100 (1)	0
Spine BMD	N=190	N=188
Week 48		
No Decrease from Baseline	97/159 (61)	52/160 (33)
≥ 3% Decrease from Baseline	16/159 (10)	43/160 (27)
≥ 5% Decrease from Baseline	7/159 (4)	7/160 (4)
≥ 3% Increase from Baseline	27/159 (17)	15/160 (9)
≥ 5% Increase from Baseline	9/159 (6)	3/160 (2)
Week 96		
No Decrease from Baseline	61/100 (61)	43/112 (38)
≥ 3% Decrease from Baseline	8/100 (8)	26/112 (23)
≥ 5% Decrease from Baseline	2/100 (2)	16/112 (14)
≥ 3% Increase from Baseline	20/100 (20)	9/112 (8)
≥ 5% Increase from Baseline	9/100 (9)	5/112 (5)

Source: Reviewer's analysis of ADDXA dataset

A separate categorical analysis assessed distribution of clinical BMD status using BMD T-scores. Normal bone status was defined by a BMD T-score ≥ −1, osteopenia by a T-score from < −1 to ≥ −2.5, and osteoporosis by a T-score < −2.5. Most subjects had normal hip and spine BMD clinical status at baseline and during the trial. At Week 48, the distribution of clinical BMD status (adjusted for baseline status) was similar between treatment groups at the hip region, but significantly different at the spine. As shown in Table 36, 2 (1%) out of the 154 subjects in the F/TAF group who had Week 48 data and who were susceptible to worsening clinical status (i.e., those in the normal and osteopenia categories at baseline) had worsening of spine BMD status at Week 48, compared with 10/156 (6%) subjects in the F/TDF group. In contrast, 8/40 (20%) subjects in the F/TAF group had improvement of spine BMD clinical status at Week 48,

compared with 4/47 (9%) of subjects in the F/TDF group. The differences between groups at Week 96 were not significant.

Table 36: Shift Table of BMD Clinical Status at Week 48 by Baseline Status (GS-US-412-2055)

	F/TAF			F/TDF		
Hip BMD	*Baseline*			*Baseline*		
	Normal (N=146)	Osteopenia (N=43)	Osteoporosis (N=1)	Normal (N=138)	Osteopenia (N=47)	Osteoporosis (N=0)
Week 48	*Number (%) of Subjects*			*Number (%) of Subjects*		
Normal	115 (96)	3 (8)	0	113 (96)	5 (12)	0
Osteopenia	5 (4)	34 (92)	0	5 (4)	35 (88)	0
Osteoporosis	0	0	1 (100)	0	0	0
Spine BMD	Baseline			Baseline		
	Normal (N=138)	Osteopenia (N=46)	Osteoporosis (N=6)	Normal (N=134)	Osteopenia (N=50)	Osteoporosis (N=4)
Week 48	*Number (%) of Subjects*			*Number (%) of Subjects*		
Normal	117 (98)	6 (17)	0	103 (91)	4 (9)	0
Osteopenia	2 (2)	29 (83)	2 (40)	10 (9)	39 (91)	0
Osteoporosis	0	0	3 (60)	0	0	4 (100)

Only subjects with nonmissing baseline BMD are included. The denominator for percentages is column total (i.e., subjects with nonmissing values at baseline and at each postbaseline visit).
Source: Reviewer's analysis of ADDXA dataset

Summary of Bone Safety

The results of the DXA substudy in Study 2055 confirm the known, but small, differences between F/TAF and F/TDF with respect to BMD changes from baseline at Week 48. The clinical relevance of these findings remains unclear as there were no notable differences between the treatment groups with respect to fracture rates or the reporting of other adverse events related to bone health.

8.5.3. Gastrointestinal Events

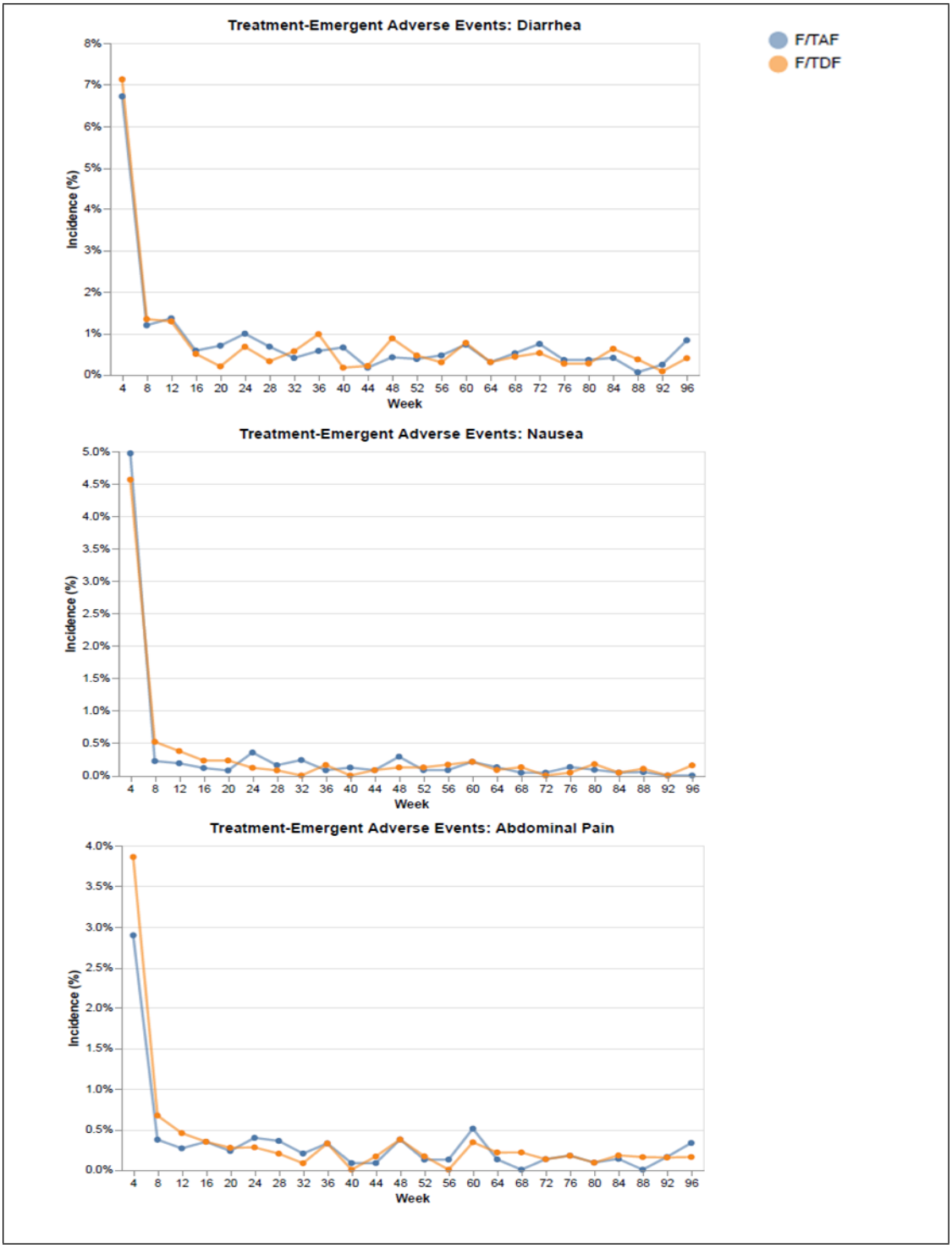
As noted in Section 8.4.5, gastrointestinal AEs were among the most common adverse reactions reported in Study 2055. Previous PrEP trials in an MSM/TGW population reported GI events occurring upon initiation of oral PrEP as part of a self-limited "start-up syndrome" {Grant et al. 2010}. As such, the incidence of nausea, diarrhea, and abdominal pain were assessed in Study 2055.

By MedDRA PT, diarrhea was reported in 16%, nausea in 7%, and abdominal pain in 3% of subjects in both treatment groups. Most TEAEs of diarrhea, nausea, and abdominal pain were Grade 1 or 2 in severity. Gastrointestinal AEs leading to premature discontinuation of study

drug, most of which were considered related to study drug, were reported in a low percentage (0.1-0.2%) of subjects in either arm.

Consistent with previous trials, diarrhea, nausea, or abdominal pain events in Study 2055 occurred with highest incidence during the first 4 weeks after the start of study drug in comparison with the remainder of the trial. By Week 8, the incidence of each event had decreased in both treatment groups and remained low through Week 96 (Figure 8). These AEs did not appear to have a noticeable impact on weight loss during the trial (see Section 8.4.7).

Figure 8: Incidence of Treatment-Emergent Gastrointestinal Adverse Events of Interest Over Time (GS-US-412-2055)



For the incidence of abdominal pain, preferred terms under the exploratory FDA MedDRA Query (FMQ) were used.
Source: FDA analysis of ADAE dataset

8.5.4. Fasting Serum Lipids

Consistent with previous clinical trials of TAF and TDF, differences were noted in Study 2055 between the F/TAF and F/TDF treatment groups with respect to changes from baseline in fasting serum lipids. In general, both arms exhibited decreases from baseline in total cholesterol and high-density lipoprotein (HDL) cholesterol at Weeks 48 and 96, as well as LDL-cholesterol at Week 96, but the magnitude of the decrease was greater in the F/TDF arm. As shown in Table 37, the median change from baseline in fasting total cholesterol at Week 48 was -1 mg/dL versus -11 mg/dL in the F/TAF and F/TDF groups, respectively. For fasting LDL-cholesterol, the median change from baseline at Week 48 was +1 mg/dL versus -6.5 mg/dL, respectively. For fasting serum triglycerides, there was a median increase from baseline of +4 mg/dL and +2 mg/dL in the F/TAF group at Weeks 48 and 96, respectively, whereas there was no change or a decrease at the corresponding time points in the F/TDF group. Importantly, there were no within group or between group differences from baseline at either time point in fasting total cholesterol to HDL ratio, which is associated with cardiovascular disease risk.

Table 37: Median Change from Baseline in Fasting Serum Lipids (GS-US-412-2055)

Lipid Parameter	Study Visit	F/TAF (N=2694)		F/TDF (N=2693)	
		N	Median	N	Median
Fasting Total Cholesterol (mg/dL)	*Baseline*	1425	173	1457	173
	Change at Week 48	1172	-1	1188	-11
	Change at Week 96	573	-4	582	-14
Fasting HDL (mg/dL)	*Baseline*	1425	49	1457	50
	Change at Week 48	1172	-2	1188	-5
	Change at Week 96	573	-1	582	-4
Fasting LDL (mg/dL)	*Baseline*	1412	99	1440	100
	Change at Week 48	1148	+1	1170	-6.5
	Change at Week 96	564	-4	575	-8
Fasting Total Cholesterol/HDL Ratio	*Baseline*	1425	3.44	1457	3.467
	Change at Week 48	1172	+0.11	1188	+0.12
	Change at Week 96	573	+0.03	582	-0.01
Fasting Triglycerides (mg/dL)	*Baseline*	1425	93	1457	93
	Change at Week 48	1172	+4	1188	0
	Change at Week 96	573	+2	582	-5

Source: Reviewer's analysis of ADLB dataset

The F/TAF group also had a higher incidence of graded treatment-emergent elevations of fasting serum total cholesterol, LDL-cholesterol, and triglycerides, across all toxicity grades, compared to the F/TDF group (Table 38).

Table 38: Treatment-Emergent Laboratory Abnormalities - Fasting Serum Lipids (GS-US-412-2055)

Laboratory Parameter		*Number (%) of Subjects*	
		F/TAF (N=2694)	F/TDF (N=2693)
Fasting cholesterol (mg/dL)		N=2371	N=2380
	Grade 1	689 (29)	466 (20)
	Grade 2	191 (8)	100 (4)
	Grade 3	20 (1)	4 (<1)
Fasting LDL (mg/dL)		N=2362	N=2377
	Grade 1	513 (22)	376 (16)
	Grade 2	141 (6)	88 (4)
	Grade 3	51 (2)	18 (1)
Fasting Triglycerides (mg/dL)		N=2371	N=2380
	Grade 2	24 (1)	15 (1)
	Grade 3	8 (<1)	4 (<1)
	Grade 4	7 (<1)	2 (<1)

Source: Reviewer's analysis of ADLB dataset

This reviewer also conducted a categorical analysis of changes from baseline in serum LDL-cholesterol based on LDL classifications from the National Cholesterol Education Program {National Institutes of Health (NIH) 2001}. By this analysis, subjects in the F/TAF group had worsening of LDL classification at Weeks 48 and 96 compared with subjects in the F/TDF group, who tended to have improvements (Table 39). At Week 48, for instance, 17% (188/1139) of subjects in the F/TAF group had worsening LDL classification compared to 10% (114/1156) of subjects in the F/TDF group. Conversely, 40% (234/587) of subjects in the F/TDF group had improved LDL classification at Week 48 compared with 28% (157/572) of subjects in the F/TAF group. Similar trends were noted at Week 96.

Table 39: Shift Table of Fasting Serum LDL Classification by Baseline NCEP Category (GS-US-412-2055)

	F/TAF (N=2694)				F/TDF (N=2693)			
	Baseline				*Baseline*			
	<100 (N=720)	100-159 (N=629)	160-190 (N=52)	>190 (N=11)	<100 (N=721)	100-159 (N=656)	160-190 (N=50)	>190 (N=17)
Week 48	*Number (%) of Subjects*				*Number (%) of Subjects*			
<100	418 (73)	126 (24)	1 (2)	1 (11)	487 (84)	192 (36)	2 (5)	2 (14)
100-159	154 (27)	371 (71)	24 (56)	0	95 (16)	325 (61)	29 (74)	6 (43)
160-190	3 (1)	22 (4)	11 (26)	5 (56)	1 (<1)	17 (3)	7 (18)	3 (21)
>190	1 (<1)	1 (<1)	7 (16)	3 (33)	0	0	1 (3)	3 (21)
Week 96	*Number (%) of Subjects*				*Number (%) of Subjects*			
<100	202 (76)	79 (29)	2 (10)	0	247 (87)	104 (39)	2 (10)	0
100-159	63 (24)	184 (67)	13 (62)	0	37 (13)	150 (57)	13 (65)	5 (71)
160-190	0	9 (3)	4 (19)	1 (50)	0	10 (4)	5 (25)	2 (29)
>190	0	4 (1)	2 (10)	1 (50)	0	0	0	0

LDL classifications adapted from the National Cholesterol Education Program.

Denominator for percentages is number of subjects with nonmissing values at baseline and postbaseline visit. Subjects with missing baseline and postbaseline values excluded.
Source: Reviewer's analysis of ADLB dataset

Importantly, the differences between the treatment groups with respect to changes in serum fasting lipids were not associated with any differences in cardiovascular or cerebrovascular events, the frequencies of which were low in both groups.

> *Reviewer comment: I reviewed the available laboratory data for 8 subjects (4 per arm) with treatment-emergent coronary artery disorders (by MedDRA HLGT). In general, these events were not associated with graded abnormalities in fasting lipid parameters.*

With that said, the proportion of subjects taking lipid modifying agents at study entry was balanced between the two arms (F/TAF 111 [4%], F/TDF 120 [5%]). However, the number and percentage of subjects who initiated lipid modifying agents during the trial were two-fold higher in the F/TAF group (N=43 [2%]) compared with the F/TDF group (N=21[1%]); per the Applicant, this difference was statistically significant (p=0.008).

8.6. Safety Analyses by Demographic Subgroups

The safety population of Study 2055 was fairly homogenous with respect to subject demographics; i.e., all subjects were biological males, the majority (84%) were White, and 75% were between 15 and 50 years of age, making conclusive statements about drug-demographic interactions difficult. Nonetheless, subgroup analyses were performed for groups defined by race (Black vs. non-Black) and age (<25, 25-50, >50 years). The proportions of subjects of other races, or of transgender women (1%), were too small for meaningful conclusions to be made.

Race

Approximately 9% of the safety population was of Black/Mixed Black race, with equal proportions in each treatment group. The median (Q1, Q3) adherence rate to study drug by pill count was 97% (91%, 100%) among Black subjects and 98% (94%, 100%) among non-Black subjects. The percentage of Black subjects experiencing any TEAE was comparable between treatment groups, but lower compared with non-Black subjects:

- TEAEs
  - Black subjects: F/TAF 81% (195/240); F/TDF 78% (182/234)
  - Non-black subjects: F/TAF 94% (2303/2454); F/TDF 94% (2312/2459)

The percentages of subjects experiencing any renal TEAE (as defined in Section 8.5.1) were comparable between Black and non-Black subjects for both treatment groups:

- Renal TEAEs
  - Black subjects: F/TAF 3% (8/240); F/TDF 4.5% (11/234)

- Non-black subjects: F/TAF 3% (71/2454); F/TDF 4% (86/2459)

Among Black subjects, the mean changes from baseline in $eGFR_{CG}$ at Week 48 by treatment group were consistent with the trends observed in the larger safety population:

- Mean (SD) change from baseline in eGFR (mL/min) at Week 48
  - Black subjects: F/TAF (N=174) +3.5 (18.7); F/TDF (N=175) -1.8 (15.0)
  - Non-black subjects: F/TAF (N=2195) +1.9 (15.6); F/TDF (N=2192) -2.0 (15.9)

Age

With respect to age, 12% of the safety population was < 25 years of age; 75% was ≥ 25 to < 50 years of age; and 13% was ≥ 50 years of age, with comparable distributions in each treatment group. Median (Q1, Q3) adherence rates (by pill count) appeared to increase slightly with each successive age group: < 25 years, 96% (89%, 99%); ≥ 25 to < 50 years, 98% (93%, 100%); ≥ 50 years, 99% (96%, 100%).

Among subjects ≥ 25 to < 50 years of age, who made up the bulk of the safety population, the proportion of subjects experiencing any TEAE was the same in both treatment groups, i.e. 93%. In the F/TAF group, TEAE rates were comparable across the different age subgroups, whereas in the F/TDF group they appeared to increase with increasing age:

- TEAEs
  - < 25 years: F/TAF 91% (307/336); F/TDF 85% (251/293)
  - ≥ 25 to < 50 years: F/TAF 93% (1892/2028); F/TDF 93% (1871/2014)
  - ≥ 50 years: F/TAF 91% (299/330); F/TDF 96% (372/386)

The proportion of subjects experiencing any renal TEAE was comparable between treatment groups across all age subgroups, and between subjects < 25 years and those 25-50 years of age. Subjects older than 50 years of age had higher frequencies of renal events, with comparable rates between treatment groups:

- Renal TEAEs
  - < 25 years: F/TAF 2% (7/336); F/TDF 2% (5/293)
  - ≥ 25 to < 50 years: F/TAF 3% (53/2028); F/TDF 3% (66/2014)
  - ≥ 50 years: F/TAF 6% (19/330); F/TDF 7% (23/386)

Differences between the F/TAF and F/TDF groups in the mean change from baseline in $eGFR_{CG}$ at Week 48 were observed at all ages; however, among subjects ≥ 50 years of age there was a smaller increase from baseline in the F/TAF group and greater decrease from baseline in the F/TDF group compared with the younger cohorts:

- Mean (SD) change from baseline in eGFR (mL/min) at Week 48
  - < 25 years: F/TAF (N=263) +2.7 (18.1); F/TDF (N=235) -1.7 (18.4)
  - ≥ 25 to < 50 years: F/TAF (N=1801) +2.1 (15.9); F/TDF (N=1767) -1.8 (16.1)

- ≥ 50 years: F/TAF (N=305) +0.8 (13.0); F/TDF (N=364) -3.2 (12.2)

With respect to bone health, consistent with the overall results of the BMD substudy, between-group differences in the mean percentage change from baseline in hip and spine BMD at Week 48 were observed in subjects at both ends of the age spectrum (Table 40). That said, subjects ≥ 50 years of age in the F/TAF group experienced a decline in hip BMD at Week 48 whereas younger subjects in the same treatment group experienced an increase, although the mean percentage changes in either direction were small. In the F/TDF group, subjects < 25 years and those ≥ 50 years of age experienced greater declines in hip and spine BMD compared to the main substudy population.

Table 40: Mean Percentage Change from Baseline in Hip and Spine BMD At Week 48 by Age Group (GS-US-412-2055)

	Hip BMD							
Age Group	<25 years		**≥25** years		>50 years		**≤50** years	
	F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF
Baseline – Mean (SD)	N=21	N=18	N=169	N=167	N=32	N=31	N=158	N=154
	1.07 (0.23)	1.05 (0.14)	1.02 (0.14)	1.02 (0.13)	1.0 (0.13)	0.99 (0.10)	1.04 (0.16)	1.04 (0.14)
Mean (SD) % Change at Week 48	N=17	N=13	N=141	N=145	N=29	N=28	N=129	N=130
	+0.29% (1.97)	-2.24% (3.0)	+0.17% (2.44)	-0.88% (2.36)	-0.28% (1.52)	-1.52% (2.57)	+0.29% (2.53)	-0.87% (2.40)
	Spine BMD							
Age Group	<25 years		**≥25** years		>50 years		**≤50** years	
	F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF
Baseline – Mean (SD)	N=21	N=18	N=169	N=170	N=33	N=32	N=157	N=156
	1.13 (0.21)	1.12 (0.13)	1.13 (0.16)	1.13 (0.14)	1.16 (0.15)	1.12 (0.12)	1.13 (0.16)	1.13 (0.14)
Mean (SD) % Change at Week 48	N=17	N=13	N=142	N=147	N=30	N=29	N=129	N=131
	+0.36% (2.84)	-2.4% (2.71)	+0.51% (3.01)	-1.01% (2.95)	+0.56% (2.60)	-1.87% (3.55)	+0.48% (3.09)	-0.95% (2.78)

Source: Reviewer's analysis of ADDXA dataset

8.7. Specific Safety Studies/Clinical Trials

No specific safety study was conducted.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

As per approved Descovy labeling, long-term carcinogenicity studies of FTC and TDF in mice and rats have not demonstrated any drug-related increases in tumor incidence at FTC and tenofovir exposures within the range of human systemic exposures at the recommended Descovy dose. (Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure is observed in rats and mice after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF.) Neither FTC nor TAF had positive findings on genotoxity studies.

In Study 2055, TEAEs in the MedDRA SOC "Neoplasms benign, malignant and unspecified (including cysts and polyps)" were reported in 160 (6%) and 136 (5%) subjects in the F/TAF and F/TDF groups, respectively. None of the 340 events was considered related to study drug by the investigators; the vast majority (96%) of events were nonserious and 82% consisted of benign skin or soft-tissue neoplasms (including penile warts). Of the remaining events, there was no clustering of any particular neoplasm or differences in frequency between the two arms.

8.8.2. Human Reproduction and Pregnancy

No new information was submitted.

Study 2055 was conducted in biological males only, thus questions about the effect of F/TAF for PrEP on human reproduction and pregnancy were not addressed in this application. The safety of F/TAF in pregnancy can be assumed to be similar between HIV-infected and non-infected individuals. Available clinical data in HIV-infected women from the Antiretroviral Pregnancy Registry (APR) show no increase in the risk of overall major birth defects for FTC compared with the background rate in a U.S. reference population; however, there are insufficient data in the APR to adequately assess the risk of major birth defects with use of TAF. Equally concerning, and relevant to a pregnant population, the efficacy of F/TAF to reduce the risk of sexually-acquired HIV-1 in cisgender women has not been established (see Section 4.5). The indication for F/TAF for PrEP, therefore, will exclude individuals at risk of HIV-1 from receptive vaginal sex. Likewise, labeling will not include language regarding the use of F/TAF for PrEP in pregnant or breastfeeding women.

While some pregnant or breastfeeding women might be at risk of HIV infection from rectal exposure, considerations regarding the use of F/TAF for PrEP in this setting would only apply to women who practice anal sex exclusively. In the absence of data regarding the prevalence of such selective practices, the likelihood seems very low and does not warrant inclusion of specific language in sections 8.1 Pregnancy or 8.2 Lactation of product labeling. Such cases are probably best handled by healthcare providers on an individual case-by-case basis, taking into account the benefit-risk balance of F/TAF in this particular scenario. In contrast, including language in labeling about the use of F/TAF for PrEP in pregnant or breastfeeding women, without providing proper context, may be confusing as it might seem to contradict the approved indication and imply an unsupported claim of efficacy against vaginal sex exposures.

8.8.3. Pediatrics and Assessment of Effects on Growth

No new information was submitted.

Consistent with the agreed-upon Initial Pediatric Study Plan (iPSP), dated December 20, 2016, the Applicant proposes to register F/TAF for PrEP for use in at-risk adolescents weighing at least 35 kg. Clinical trials to evaluate the safety and efficacy of F/TAF for a PrEP indication have not been conducted in adolescents. Instead, the Applicant proposes to extrapolate adult PrEP efficacy data from Study 2055 in MSM/TGW and available safety and PK data with F/TAF in HIV-infected pediatric subjects to support an adolescent indication.

While no PK studies were conducted in adolescents for this indication, the dose of F/TAF is the same for adolescents and adults, and available data suggest that there are no clinically relevant differences in the plasma PK of FTC or TAF, or in PBMC-associated TFV-DP exposures, between HIV-infected adolescents weighing at least 35 kg and HIV-infected adults. Likewise, there are no clinically relevant PK differences between HIV-infected and non-infected adults. Therefore, it is reasonable to expect that PK parameters will be similar between non-infected adolescents and non-infected adults, thus allowing for the extrapolation of adult PrEP efficacy data. This extrapolation approach is also scientifically valid because sexual acquisition of HIV-1 is similar between adults and adolescents. Safety in adolescents is supported by findings from Study 2055 and other clinical trials of F/TAF in HIV-infected pediatric subjects. Taken together, based on PK and clinical considerations, it is reasonable to expand the PrEP indication to include adolescents weighing at least 35 kg. As discussed in Section 4.5, however, efficacy in MSM/TGW cannot be extrapolated to cisgender women based on the available PK data; therefore, the adult efficacy data from Study 2055 cannot be extrapolated to support an indication in female adolescents. This limitation to the adolescent indication will be noted in Descovy labeling.

A partial waiver request for studies in infants and children up to 12 years of age was submitted with this application. As PrEP is intended to reduce the risk of sexually-acquired HIV-1 infection, clinical efficacy trials would be highly impracticable in a younger pediatric population who are not sexually mature and active, or in whom the likelihood of at-risk sexual behavior is very low.

A meeting of the FDA Pediatric Research Committee (PeRC) was held on September 4, 2019, to discuss this application. The PeRC agreed to grant the requested waiver in children from birth to < 12 years of age and concurred with the extrapolation approach to support the use of F/TAF for PrEP in at-risk adolescents, excluding those at risk from receptive vaginal sex, weighing at least 35 kg.

Lastly, while F/TAF safety and efficacy data can be reasonably extrapolated from other sources, adherence to a daily oral PrEP regimen is likely to differ between at-risk adolescents and their adult counterparts in Study 2055. In two previously conducted open-label trials of F/TDF for

PrEP in adolescents, the ATN 113 trial in MSM aged 15-17 years in the U.S. {Hosek et al. 2017} and the Choices for Adolescent Prevention Methods for South Africa (CHAMPS) PlusPills trial in South African boys and girls aged 15-19 years (NCT02213328) {Gill et al. 2017}, a trend toward lower adherence to a daily oral PrEP regimen was observed as study visits became less frequent, suggesting that monthly visits may be needed to support greater adherence among adolescents. These insights into adolescent adherence, as gleaned from the ATN 113 trial, informed Truvada labeling in 2018 {Gilead Sciences, Inc. 2018}, and can be transferred to Descovy labeling as both drugs share the same once daily dosage schedule.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No new safety issues have been identified from the available data regarding overdose. No new information regarding drug abuse potential, withdrawal, or rebound was submitted, but drug abuse is not expected with F/TAF for PrEP.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Descovy was approved for the treatment of HIV-1 infection in 2016. Since first marketing approval, the cumulative exposure to drug product is estimated to be (b) (4) patient-years of treatment. In addition, TAF has been marketed in various fixed-dose combination products for an HIV-1 treatment indication since at least 2015, and as monotherapy for the treatment of chronic hepatitis B infection since 2016. In general, TAF and F/TAF have been well-tolerated in the postmarket period, and no major new safety issues have emerged based on periodic safety update reports (PSURs) and periodic benefit-risk evaluation reports (PBRERs) submitted to this and other NDAs for TAF-containing products. The overall benefit-risk assessment for F/TAF remains positive.

That said, per the most recent Periodic Adverse Drug Experience Report (PADER) submitted to this NDA (dated January 21, 2019), rash, urticaria, and angioedema have been identified as adverse reactions to TAF in postmarketing. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have already been added to Section 6.2 (Postmarketing Experience) of labeling for other TAF-containing products (e.g., Vemlidy, Genvoya, Biktarvy) and will be added to Descovy labeling as part of this application.

In Study 2055, 6% of subjects in each treatment arm experienced an allergic-type TEAE under the MedDRA SOC “Skin and subcutaneous tissue disorders”, including rash, urticaria, and angioedema. The vast majority (91%) of these events were not considered related to study drugs by the investigators. The frequencies of these events by MedDRA HLT were comparable between the treatment groups, and no between-group differences were noted when SMQs

(broad and narrow) of severe cutaneous adverse reaction, anaphylactic reaction, or angioedema were analyzed. About 20% of these events occurred within the first 30 days of study drug administration, with comparable distributions in both arms; however, of these early onset events, 36% (15/40) in the F/TAF group versus 19% (7/36) in the F/TDF group were considered related to study drug by the investigators. Five subjects had nonserious skin events that led to study drug discontinuation within the first 30 days of administration: 4 subjects with rash (2 per treatment group), and 1 subject with generalized pruritus in the F/TDF group; all but one case of rash in the F/TDF group were considered related to study drug.

One subject in the F/TDF arm (Subject (b) (6)) also experienced a serious Grade 2 event of Stevens-Johnson syndrome on Day 5. The event was not considered related to study drug and did not result in study drug discontinuation (only interruption). The subject had initiated treatment for syphilis with doxycycline on Day 1, which might provide an alternative etiology.

8.9.2. Expectations on Safety in the Postmarket Setting

As HIV-1 infection status has no clinically relevant impact on the PK of FTC and TAF and given the favorable safety profile of other F/TAF-containing products on the market when used for HIV-1 treatment, the safety profile of F/TAF for HIV-1 PrEP is also expected to be favorable in the postmarket setting. Safety issues related to renal and bone toxicity, and increases in fasting lipid parameters and body weight, should continue to be monitored.

8.9.3. Additional Safety Issues From Other Disciplines

None identified.

8.10. Integrated Assessment of Safety

In Study 2055, once-daily F/TAF for PrEP was well tolerated in 2,694 healthy participants, with a median exposure of 86 weeks, as demonstrated by the low proportions of subjects with study drug-related SAEs (0.1%) or TEAEs leading to study drug discontinuation (1.3%). The most common, non-infectious TEAEs, with an incidence of ≥ 5%, in subjects randomized to F/TAF were diarrhea (16%), nausea (7%), headache (7%), and fatigue (5%); the most common drug-related TEAEs, or ARs, with an incidence ≥ 2%, were diarrhea (5%), nausea (4%), fatigue, headache, and abdominal pain (2% each). Most TEAEs reported in this trial were mild (Grade 1). For all of the above safety findings, and indeed for nearly all reported adverse events, there were no notable differences between the F/TAF and F/TDF groups. The safety findings reported in this trial, in particular those related to subclinical changes in renal biomarkers and bone density, are consistent with previous trials that have compared TAF to TDF. Moreover, the safety profile of F/TAF in HIV-uninfected participants was similar to that reported for PLWH; i.e., no new safety concerns were identified.

The important safety issues identified in this review are as follows:

Nephrotoxicity: Higher plasma concentrations of TFV, as seen with TDF administration, have been associated with nephrotoxicity. Conversely, lower circulating TFV levels, as seen with TAF, are hypothesized to result in fewer renal adverse events. In Study 2055, small but significant differences were observed at each visit between the treatment groups with respect to changes from baseline in serum creatinine and $eGFR_{CG}$, favoring F/TAF. In addition, F/TAF was noted to have favorable effects on changes from baseline at Week 48 in numerous renal biomarkers of proximal tubular function (UPCR, β2M and RBP to creatinine ratios) relative to F/TDF, although the clinical significance of these changes is uncertain. While there were no reports of PRT in the F/TAF group (compared to one case of Fanconi syndrome in the F/TDF group), the overall rates of renal-associated TEAEs, SAEs, or events leading to drug discontinuation, as well as of graded renal laboratory abnormalities, were low but generally comparable between the treatment groups. It is possible that with longer duration of use these differences in renal biomarkers may translate into improved renal clinical outcomes, but this remains mostly speculative at the moment. That said, given the substantial rates of PrEP non-persistence being reported beyond one year, it is unclear how relevant these subclinical changes will be to an HIV-uninfected population that may only be using F/TAF for PrEP for a limited duration {Coy et al. 2019}. In sum, the renal safety profile of F/TAF is certainly no worse than that of F/TDF, but whether its favorable biomarker profile translates into clinical benefit remains to be determined. For now, product labeling for F/TAF will retain the warning and precaution related to renal impairment (5.3). Routine laboratory monitoring as recommended in labeling should suffice to manage this potential safety risk.

Bone Mineral Density Changes: Available preclinical and clinical data suggest that TDF use is associated with reductions in BMD. The clinical significance of this for most individuals remains unclear as reports have been mixed about a possible association between TDF use and fragility fractures {Grant et al. 2016}. Consistent with previous trials, Study 2055 demonstrated small, but statistically significant differences between F/TAF and F/TDF with respect to BMD changes from baseline at 48 weeks, favoring F/TAF. The improvements in BMD seen with F/TAF were observed across all age subgroups. Clinically, there were no differences between the treatment groups with respect to fracture rates or the reporting of other events related to bone health. Given the uncertain relationship between BMD reductions and fracture risk, labeling for F/TAF and other TAF-containing products no longer includes a warning related to bone loss, but BMD changes are still reported in Section 6 Adverse Reactions. Product labeling is considered adequate to convey this potential safety risk.

Fasting Serum Lipid Changes: Consistent with previous clinical trials, Study 2055 demonstrated differences between F/TAF and F/TDF in serum fasting lipid changes from baseline, favoring F/TDF. Higher proportions of subjects in the F/TAF group also had graded increases in fasting total cholesterol or LDL cholesterol during the course of the trial compared with the F/TDF

group. The reasons for these differences have not been fully elucidated but circulating TFV has been hypothesized to have lipid-lowering properties. As TAF administration results in lower TFV plasma concentrations, per this hypothesis F/TAF would have less of an impact on countering increasing lipid levels over time than F/TDF. The clinical significance of these differences is not entirely clear as there were no between-group differences in fasting total cholesterol to HDL ratio, which is associated with cardiovascular risk, or in cardiovascular or cerebrovascular events, which were rare. Moreover, the percentage of subjects initiating lipid-lowering agents during the trial was low in both arms (1-2%). Labeling for F/TAF will describe the fasting lipid changes observed in Study 2055 in Section 6 Adverse Reactions, consistent with labeling of other TAF-containing products. Product labeling is considered adequate to manage this potential safety risk.

Body Weight Increase: Although subjects in the F/TAF group of Study 2055 experienced a mean increase of 1.1 kg in body weight at 48 weeks, in contrast to no change in the F/TDF group, this increase appears to be consistent with expected weight gains in a healthy population between 20 and 40 years of age. Rather than F/TAF directly causing increased weight, the differences in weight changes between the treatment groups of Study 2055 may be due to a suppressive effect of F/TDF on expected weight gain in this population. As such, based on the data from Study 2055, there does not appear to be an F/TAF-related risk of weight increase in the HIV-uninfected male population evaluated in this trial.

Conclusion

The F/TAF safety data reviewed as part of this application are consistent with previous clinical trials that showed improved measures of renal tubular function (as demonstrated by changes in urinary biomarkers over time) and minimal impact on BMD (as observed on DXA imaging) with TAF dosing relative to TDF. While these subclinical differences were statistically significant, and favored F/TAF, the clinical benefit of F/TAF over F/TDF was not apparent in the context of a 96-week trial, where no clinically-relevant differences were noted between F/TAF and F/TDF in the frequency or types of adverse events related to renal or bone safety, or in the frequency or severity of abnormalities for most laboratory tests commonly used in clinical practice. Indeed, the clinical safety profile of F/TAF and F/TDF were remarkably similar in Study 2055 with respect to common adverse events, SAEs or adverse events leading to drug discontinuation (the latter two of which occurred at very low rates). These findings are consistent with a recent meta-analysis of 11 trials that compared TAF to TDF {Hill et al. 2018}. Also consistent with previous trials, there was a higher incidence of elevated fasting lipids in Study 2055 among subjects taking F/TAF compared with those taking F/TDF; however, these findings were not associated with greater cardiovascular risk in this relatively short-term trial. Finally, the potential safety risks identified for F/TAF in this review are not new and most are not serious; they can be adequately managed through product labeling and routine pharmacovigilance.

9. Advisory Committee Meeting and Other External Consultations

A meeting of the Antimicrobial Drug Advisory Committee (AMDAC) was held on August 7, 2019, to discuss this supplemental application. The main objective was to discuss whether the available data supported approval of F/TAF for HIV-1 PrEP in at-risk adults and adolescents. In particular, the FDA was interested in the committee's input regarding the adequacy of the data to support a PrEP indication in subpopulations defined by route of HIV transmission risk (i.e., receptive anal intercourse, insertive penile intercourse, and receptive vaginal intercourse). With respect to the latter, as clinical data with F/TAF for PrEP in cisgender women are lacking, the FDA sought advice on the acceptability of the PK extrapolation strategy proposed by the Applicant to support the broad indication being sought.

The AMDAC voted 16-2 in support of approval of F/TAF for PrEP in MSM/TGW. The two committee members who opposed approval cited insufficient data in TGW and African-Americans, who are disproportionally affected by HIV in the United States. The ADMAC noted the importance of F/TAF being noninferior, but not superior, to F/TDF in Study 2055, and advised that product labeling should explicitly convey that finding. Some committee members expressed concern about the elevated serum lipids and weight gain observed with F/TAF and considered that these should be followed closely in the postmarket setting, along with collection of longer-term data concerning kidney and bone safety.

The AMDAC, however, voted 10-8 against approval in cisgender women (or those at risk of HIV-1 from receptive vaginal sex). The PK data failed to sway the majority of committee members, who were not entirely convinced by the Applicant's assertion that systemic drug exposure alone drives PrEP efficacy. Most of those who voted in favor of an approval in cisgender women did so mostly out of concern that a limited approval would set up a two-tier system and exacerbate gender inequities in health care. Regardless of how they voted, the committee was unanimous in voicing a need for high-quality clinical trial data in cisgender women, and some members expressed disappointment that an application for an HIV-1 PrEP agent would be submitted without such data. The Applicant stated at the meeting that it was committed to study F/TAF for PrEP in a female population.

Lastly, the AMDAC concurred that data from Study 2055 could be applied to men at risk of HIV-1 from insertive (vaginal or rectal) sex.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

U.S. Prescribing Information

The draft U.S. Prescribing Information (USPI) for Descovy, received April 5, 2019, was reviewed and revised as follows (refer to final labeling for details):

Labeling Section	FDA Comment
All Sections	In general, the information contained in the USPI was accurate; however, where the presentation of information was considered misleading or promotional, FDA proposed alternate language. Much of the language related to the PrEP indication mirrors that of the approved Truvada USPI.
INDICATIONS AND USAGE	The Applicant's proposed indicated population for PrEP (i.e., at-risk adults and adolescents weighing at least 35 kg) was inappropriately broader than the studied population. Specifically, the efficacy of F/TAF for PrEP in cisgender women could not supported by the totality of the evidence (see Section 4.5). As such, FDA limited the PrEP indication for Descovy by excluding individual at risk of HIV-1 acquisition from receptive vaginal sex. A Limitation of Use statement was considered reasonable to alert prescribers that effectiveness in this population has not been evaluated. Moreover, in contrast to the Truvada indication, the PrEP indication for Descovy does not include "in combination with safer sex practices" as this is not reflective of how the product was used in the pivotal trial or how PrEP is generally used in practice. Further information about the proper use of Descovy for PrEP is included in the Warnings and Precautions subsection 5.2
DOSAGE AND ADMINISTRATION	The Applicant's revisions to this section were appropriate and aligned with recommendations found in the Truvada USPI
BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS	A new Boxed Warning and Contraindication were proposed to align with the approved Truvada PI. A new Warning and Precaution 5.2 – Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When Descovy is Used for HIV-1 PrEP – was included. Much of the information is consistent with the corresponding warning in the Truvada USPI but streamlined in some areas (e.g., discussion of HIV-1 risk factors) given the greater familiarity with PrEP since the time of the Truvada approval. Given that wording regarding safer sex practices is not part of the PrEP indication for Descovy, FDA considered it prudent to include a statement that the time from initiation of Descovy to maximal protection against HIV-1 infection is unknown.
ADVERSE REACTIONS	The proposed Clinical Trials Experience subsection describes the rates of common ARs in Study 2055; FDA added abdominal pain, which was omitted

	from the Applicant's proposal due to splitting of preferred terms. Changes from baseline at Week 48 in serum creatinine, $eGFR_{CG}$, UPCR and BMD are also described. The FDA did not agree with the inclusion of information related to exploratory renal biomarkers (e.g. β2M or RBP) or the use of ≥ 3% change from baseline to describe the BMD changes, preferring to use ≥ 7% and ≥ 5% cutoffs for the hip and spine regions, respectively (see Table 35), which the FDA considers to be more clinically meaningful. In addition, FDA recommended including the changes from baseline in fasting serum lipids. Lastly, the Postmarketing Experience subsection (6.2) was updated to include the terms angioedema, urticaria, and rash (see Section 8.9.1).
USE IN SPECIFIC POPULATIONS	The FDA did not agree with the Applicant's proposals to update Sections 8.1 Pregnancy and 8.2 Lactation with PrEP-related information given the Descovy indication excludes persons at risk from receptive vaginal sex. The language proposed for Section 8.4 Pediatric Use was appropriate.
CLINICAL PHARMACOLOGY	The Applicant's proposal to update Section 12.4 Microbiology with data from the CDC rectal challenge macaque study with F/TAF was appropriate; however, the FDA did not agree with (b) (4) given the limited PrEP indication being approved.
CLINICAL STUDIES	The important design features and baseline disease characteristics of Study 2055 were included, as well as description of the high STI rates observed during the trial. The section provides a fair representation of the overall efficacy results (i.e. noninferiority of Descovy to Truvada in reducing the risk of HIV-1) and subgroup analyses. FDA simplified the proposed language regarding drug adherence (from the DBS case-control substudy) to note that subjects who became HIV-infected had substantially lower median intracellular levels of TFV-DP compared with matched HIV-uninfected controls, removing (b) (4)

Medication Guide

The Patient Package Insert (PPI) for Descovy was converted to a Medication Guide (MG) with this application. The proposed revisions were largely consistent with the Descovy USPI and the Truvada MG; however, FDA revised language to emphasize the limitations of use, namely that Descovy for PrEP is not indicated for use in biological females at risk of HIV-1 acquisition from receptive vaginal sex. Refer to the FDA Patient Labeling Review for details.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

The main risk associated with any antiretroviral drug used for PrEP is that the product will be initiated or continued in the face of undiagnosed HIV-1 infection, thus increasing the risk of developing drug resistance. This was the concern that led to the creation of a Risk Evaluation and Mitigation Strategy (REMS) when F/TDF was approved for PrEP in 2012. That REMS initially consisted of a Medication Guide, communication plan, a timetable for assessments of the REMS, and elements to ensure safe use (ETASU), the latter of which consisted of educational and training materials made available for voluntary use by prescribers and users of PrEP.

At the time of the initial PrEP approval, public information and awareness of PrEP were very limited and a REMS was considered necessary to ensure that the benefits outweighed the risks. In the last five years, however, awareness and uptake of PrEP have increased substantially. The reasons for this are manifold but undoubtedly include the proliferation of external resources, from the CDC to state and city health departments to advocacy groups, that have provided educational materials about PrEP, issued PrEP clinical guidelines, and promoted PrEP use among high-risk individuals. Importantly, knowledge about the risks and appropriate use of PrEP among prescribers and users has increased to satisfactorily levels during this period, as demonstrated by surveys conducted for the periodic REMS assessments. Whether survey respondents obtained their information from the REMS or other external sources is not clear. Regardless, based on the availability of multiple non-REMS educational programs, the publication of PrEP clinical guidelines by the CDC and other health authorities, and the acceptable levels of PrEP knowledge demonstrated by prescribers and users, the FDA determined in 2019 that a REMS was no longer necessary to maintain a favorable benefit-risk balance. The REMS for F/TDF for PrEP was released on July 1, 2019, although the Medication Guide remains part of product labeling [refer to the REMS reviews for NDA 21752/S-060 by the Division of Antiviral Products (DAVP) and Division of Risk Management (DRISK)].

The above considerations also apply to F/TAF for PrEP. As such, a REMS is not deemed necessary to manage the potential risks associated with use of F/TAF for PrEP, which can be adequately managed in the postmarket setting through labeling, including a Medication Guide.

12. Postmarketing Requirements and Commitments

The data submitted in this application have met the statutory requirements to support a PrEP indication for F/TAF in individuals at risk of HIV-1 acquisition from receptive anal intercourse or insertive penile intercourse and are thus sufficient to allow for regulatory action to be taken. However, data that convincingly demonstrate the efficacy of F/TAF for PrEP in individuals at risk of HIV-1 from receptive vaginal intercourse (e.g., cisgender women) are lacking. The PrEP indication for F/TAF will therefore exclude this population and product labeling will note this limitation of use.

The availability of additional HIV prevention options for at-risk women is of paramount importance to global efforts to curb the HIV epidemic. At the AMDAC meeting, committee members were unanimous in their call for clinical trial data in cisgender women to evaluate the safety and effectiveness of F/TAF for PrEP in that population. Depending on how they voted, the ADMAC members considered that these data could be collected pre- or post-approval. Given that this application is ready for approval, albeit with a limited indication, and that an approved safe and effective drug (F/TDF) is currently available for use in at-risk women, rather than delay the approval of this application, the FDA has determined that a clinical trial of F/TAF for PrEP in cisgender women can be conducted as a postmarketing commitment.

The FDA is cognizant of the challenges in designing a feasible PrEP trial in cisgender women. At the time of this writing, discussions were underway with the Applicant to explore novel trial designs that could support an expanded indication in this population. While details are still being negotiated, FDA is requesting a randomized trial in at-risk women and adolescent girls with F/TDF as a control. The trial, however, would be powered to demonstrate efficacy relative to background HIV-1 incidence rates as estimated by at least two distinct methods, such as the background HIV-1 incidence rates from sites involved in recent clinical trials, cross-sectional HIV surveillance surveys, or from high-quality local epidemiology data. Given this is novel approach to estimating PrEP efficacy in a clinical trial setting, two distinct external controls would serve to corroborate the observed treatment effect and increase confidence in the results.

13. Appendices

13.1. GS-US-412-2055 Study Procedures

			Double-Blind Treatment End of Week[a]									Post Week 96	Open-Label Treatment End of Week[c]							
Study Procedure	Screening	Day 1	4	12	24	36	48	60	72	84	96	Every 12 Weeks	End of Blinded Treatment Phase Visit[b]	12	24	36	48	Every 12 Weeks[d]	30-Day Follow-up[e]	ESDD[f]
Informed Consent	X																			
Medical History	X																			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X						X				X						X			
Targeted Physical Exam		X[g]	X	X	X	X		X	X	X		X	X	X	X	X		X	X	X
Vital Signs[g]	X	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																			
Genital, Rectal, and Pharyngeal Examination for STIs as appropriate	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharyngeal Swab for Gonorrhea and Chlamydia[a,c] (Local Laboratory)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rectal Swab for Gonorrhea and Chlamydia (Local Laboratory)[a,c]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample for Gonorrhea and Chlamydia	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rapid HIV-1 Ag/Ab Test (In-Clinic)[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 Ab/Ag[q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 RNA by PCR[r]	X	X[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dipstick Urinalysis (In-Clinic)	X																			
Urinalysis, Urine Protein, Urine Chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Storage Sample			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Chemistry Profile[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Hematology Profile[i]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for DBS[j]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood Sample for Syphilis testing[k] (Local Laboratory)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B Testing (HBsAg/HBsAb/HBcAb)	X				X		X		X		X	X[a,l]	X[a,l]		X		X	X[a,l]		
Hepatitis C Testing (HCV Ab)	X						X				X	X[a,c]	X[a,c]				X	X[a,c]		
Estimated GFR	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Lipids (fasting not required at screening)	X				X		X		X		X	X[t]			X		X	X[t]		
Trough PK blood sample (PBMC and plasma)[j]			X																	
Anytime PK blood sample (plasma only)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Plasma Storage Sample[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

			Double-Blind Treatment End of Week[a]									Post Week 96	Open-Label Treatment End of Week[c]							
Study Procedure	Screening	Day 1	4	12	24	36	48	60	72	84	96	Every 12 Weeks	End of Blinded Treatment Phase Visit[b]	12	24	36	48	Every 12 Weeks[d]	30-Day Follow-up[e]	ESDD[f]
CASI Questionnaire[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Randomization in IXRS		X																		
Risk Reduction/ Adherence Counseling	X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
DXA Scan (Hip and Spine)		X[p]					X[q]				X[q]		X[q]				X[q]			X[r]
Study Drug Dispensation and Accountability		X[s]	X	X	X	X	X	X	X	X	X	X	X[t]	X	X	X	X[uv]	X		X[wb]
CD4, CD8, and CD4/CD8 (HIV Infected Only)			Performed at all visits after HIV infection.																X	X
Latent and Active Reservoir assessment (HIV Infected Only)			Performed for HIV infected participants only. Performed at first study visit after HIV infection and at regularly scheduled study visits 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter.																	X
T cell response and phenotype (HIV Infected Only)			Performed for HIV infected participants only. Performed at first study visit after HIV infection and at regularly scheduled study visits 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter.																	X
Viral Sequence Diversity assessment (HIV Infected Only)			Performed for HIV infected participants only. Performed at first study visit after HIV infection and at regularly scheduled study visit 24 weeks after HIV infection only.																	X
Inflammatory/Immune Activation Biomarkers (HIV Infected Only)			Performed for HIV infected participants only. Performed at first study visit after HIV infection and at regularly scheduled study visits 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter.																	X

Source: Interim Clinical Study Report for Study GS-US-412-2055

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Guidances for Industry

Guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Systemic Drug Products for Pre-Exposure Prophylaxis* (March 2019)

13.3. Financial Disclosure

In accordance with 21 CFR 54.4, the Applicant has submitted the Financial Certification and Disclosure summary information for all investigators who participated in the covered clinical study for this application, Study GS-US-412-2055.

Covered Clinical Study (Name and/or Number): Study GS-US-412-2055 (DISCOVER)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 673		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 42		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 2 Significant payments of other sorts: 36 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 4		
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: Not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

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.

/s/

PETER S MIELE
10/02/2019 10:28:40 AM

WENDY W CARTER
10/02/2019 10:46:59 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208215Orig1s012

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	208,215 / S-0012
Drug Name:	DESCOVY (Emtricitabine/Tenofovir Alafenamide; F/TAF or DVY)
Indication(s):	Pre-exposure prophylaxis (PrEP) of human immunodeficiency virus type 1 (HIV-1) infection
Applicant:	Gilead Science, Inc.
Date(s):	Submitted: April 4, 2019 Received: April 5, 2019 PDUFA Date: October 5, 2019 Draft Review Completed: August 31, 2019 Final Review Completed: September 10, 2019
Review Priority	Priority
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Wen Zeng, Ph.D.
Concurring Reviewers:	Thamban Valappil, Ph.D. , Statistical Team Leader
Medical Division:	Division of Antiviral Drug Products (HFD-530)
Clinical Team:	Peter Miele, MD; Medical Reviewer Wendy Carter, D.O.; Medical Team Leader
Project Manager:	Alicia Moruf, PharmD

Keywords: DESCOVY, DVY, F/TAF, Pre-exposure prophylaxis (PrEP), HIV-1 Infection, Men and transgender women who had sex with men (MSM/TGW).

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1. EXECUTIVE SUMMARY

Descovy (DVY or F/TAF) is a fixed-dosed combination tablet containing emtricitabine (FTC) 200 mg and tenofovir alafenamide (TAF) 25 mg, and both are HIV nucleoside analog reverse transcriptase inhibitors (NRTIs). Descovy was approved in 2016 as a part of a complete regimen for treatment of chronic HIV-1 infection in adults and pediatric patients weighing at least 35 kg. In this submission, the Applicant seeks to extend the indication of Descovy for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition in adults and adolescents weighing at least 35 kg.

For HIV-1 PrEP, FDA approved the fixed-dose combination of FTC 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg (Truvada®, F/TDF, or TVD) to reduce the risk of sexually-acquired HIV-1 infection in at-risk adults, in 2012. The PrEP indication for Truvada was expanded to include at-risk adolescents weighing at least 35 kg in 2018.

Tenofovir disoproxil fumarate (TDF) is a prodrug hydrolyzed to tenofovir (TFV) which circulates in plasma. The TAF prodrug is also hydrolyzed to TFV in plasma but this occurs much more slowly than TDF in plasma. Because one prodrug of TFV has already been approved for this indication and F/TAF has already approved for HIV-1 treatment, one phase 3 trial was considered as sufficient to support this sNDA submission.

The Applicant submitted one phase 3 trial, GS-US-412-2055 (DISCOVER), to support the evaluation of Descovy for PrEP of HIV-1 infection in at-risk adults and adolescents. The DISCOVER trial is an ongoing multinational, randomized, double-blind trial to compare the safety and efficacy of F/TAF versus F/TDF in HIV-1 negative adult men and transgender women who have sex with men (MSM/TGW) and are at high risk of HIV-1 infection. The trial is being conducted in 94 sites across 11 countries in North America and the European Union in cities known to be historic urban epicenters of the HIV epidemic and with high prevalence of people living with HIV, as well as in cities where new HIV cases are increasing, and where HIV-associated sexual risk behavior is high. The primary efficacy endpoint was the rate of HIV-1 infection in MSM/TGW who were administered daily F/TAF or F/TDF with a minimum follow-up of 48 weeks and at least 50% of subjects have 96 weeks of follow-up after randomization. This was a non-inferiority (NI) design and the NI margin of 1.62 was determined from three historical trials with 50% preservation of F/TDF benefit over placebo.

A total 5399 subjects were randomized using 1:1 ratio to either F/TAF or F/TDF arm. The primary efficacy analysis was based on the full-analysis set (FAS), which included 5335 subjects who were randomized, dosed, not HIV-1 positive on Study Day 1, and had at least one post-baseline HIV laboratory assessment. Twenty-two (0.4%) of 5335 subjects in the FAS were infected with HIV-1 during the trial, of which, 7 were in the F/TAF arm and 15 were in the F/TDF arm. The HIV-1 infection rates were 0.160 per 100 person-years (PY) and 0.342 per 100 person-years in F/TAF arm and F/TDF arm respectively. The upper bound of the 95.003% confidence interval (CI) of the rate ratio of F/TAF vs. F/TDF was 1.149, which was lower than the pre-specified NI margin of 1.62. Therefore, the trial demonstrated that F/TAF was non-inferior to F/TDF in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population.

The Applicant sought a broad indication to include cisgender women and adolescent. Thus, the Applicant also submitted two extrapolation reports, one for cis-gender women and one for adolescents, to support Descovy for PrEP in women and adolescents. An advisory committee (AC) meeting was hold on August 7, 2019 to discuss these. Please see other discipline's reviews for details and the impact on the final indication.

Key statistical issue: The NI margin.

The NI margin used in this trial was determined from three historical trials with F/TDF vs. placebo for PrEP in MSM population (Table 1 below).

Table 1: Efficacy Information from Truvada as PrEP in MSMs

Clinical Trial	Sample Size Placebo (PY Follow-Up)	Sample Size F/TDF (PY Follow-Up)	HIV Infections (Incidence per 100 PY [95% CI])		Rate Ratios in HIV Infection Rates, per 100 PY [95% CI]	Enrolment
			PBO	F/TDF		
iPrEX (URAI subgroup) at screening	753 (1054)	732 (1055)	56 (5.3) [4.0, 6.8]	23 (2.2) [1.4, 3.2]	2.4 [1.5, 3.9]	July 10, 2007 - Dec 17, 2009
PROUD	255 (222)	268 (243)	20 (9.0) [5.6, 13.4]	3 (1.2) [0.3, 3.5]	7.3 [2.2, 24.2]	Nov 29, 2012 – Apr 30, 2014
IPERGAY	201 (212)	199 (220)	14 (6.6) [3.9, 10.6]	2 (0.9) [0.2, 3.2]	7.3 [1.7, 31.6]	Feb 22, 2012 – Oct 23, 2014
Pool	1209 (1488)	1199 (1518)	90 (6.0) [4.9, 7.5] {6.96}*	28 (1.9) [1.3, 2.6] {1.44}*	5.1* [2.64, 9.70]*	

Source: iPrEX from {Grant 2010}; IPERGAY from {Molina 2015}; PROUD from {McCormack 2015}

* The pooled incidence rate for placebo and F/TDF, based on equal weighting of three studies, are within {} which are used for estimating the rate ratio and its 95% CI.

Source: Table 1-1 in statistical analysis plan (SAP) for this study.

Based on these three historical trials, the Applicant estimated the weighted pooled HIV-1 incidence rate for F/TDF to be 1.44 per 100 PY, and the rate ratio compared to placebo was 5.1 per 100 PY and the lower bound of the 95% CI was 2.64. The NI margin of 1.62 was determined based on the square-root of 2.64, 50% preservation of the F/TDF effect over placebo. Consequently, a sample size of 2500 in each arm (1:1 randomization) provides at least 82% power to show F/TAF is non-inferior to F/TDF with respect to the HIV-1 infection rate.

The infection rate in F/TDF arm in the current trial was 0.342 per 100 PY, which is approximately 4-folder lower than expected infection rate of 1.44 per 100 PY based on the

historical data. This raises question(s) about the validity of the constancy assumption of the control effect over placebo and the possible need to adjust the NI margin.

One possible explanation for the lower infection rate in the F/TDF arm in the current trial compared to that observed in the historical trials is the higher adherence rate of F/TDF in the current trial. According to the study report, the median self-reported adherence was greater than 95% at all visits by computer-assisted self-interview (CASI) questionnaire and mean of pill-count adherence was 93% in both treatment arms. In the dried blood spot (DBS) substudy, most subjects in both arms had tenofovir diphosphate (TFV-DP) levels in red blood cells consistent with high adherence (≥ 4 days of dosing per week).

Additionally, we do not have any direct information about the infection rate of the non-existent or putative placebo arm. If we assume a proportional change for placebo to that observed in the control arm, the unknown placebo incidence rate may have also reduced by 4-fold from the historical rate corresponding to F/TDF. This scenario may also require an assumption that the sexual partner's risk to infect was unchanged during the trial. Note that the interpretability of findings could be impacted if the unknown placebo incidence rate is much lower than the proportional change in the current trial. The Applicant did summarize the 2016 CDC infection data in non-study PrEP-eligible MSM at risk of HIV-1 in 25 US metropolitan statistical areas (MSAs), which are overlapping with GS-US-412-2055 sites. The infection rate was 4.02 per 100 PY with 95% CI of [3.56, 3.66].

Based on the above explanations, if we believe that the infection rate in the placebo arm is less than the 4-fold decrease from historical rate, there is no need to adjust the current NI margin as the primary analysis used a rate ratio metric. From the perspective of the reviewer, the rate ratio metric is more stable for any reduction in the event rate of the active control arm compared to rate difference approach.

A sensitivity analysis was performed to evaluate the impact on the findings if the non-inferiority margin was re-adjusted to account for the lower observed HIV-1 incidence rate in the F/TDF arm. The re-adjusted non-inferiority margin was 1.13, which was the quadratic-root of the original NI margin, and the upper bound of the 95.003% CI of the rate ratio of F/TAF versus F/TDF (1.149) falls slightly outside the margin. This is one potential way to adjust the NI margin if there are other concerns on the validity of the historical evidence of treatment effect, although it is conservative.

Overall, the reviewer concludes that the original NI margin of 1.62 is applicable in this case and the trial demonstrated that F/TAF was non-inferior to F/TDF in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population.

2. INTRODUCTION

2.1 Overview

2.1.1 The Study Reviewed

The description of the study is listed in Table 2. Study GS-US-412-2055 (DISCOVER) was conducted in 94 sites across 11 countries, Austria, Canada, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, United Kingdom, and United States. The detailed design characteristics of the phase 3 study are described in section 3.2.1.

Table 2 Phase 3 trial design details included in this review

Study	Phase and Design	Objectives/Primary Endpoint	Treatment Period	# of Subjects per Arm	Study Population
GS-US-412-2055	A phase 3, double-blind, randomized, active-controlled study to evaluate the safety and efficacy of F/TAF QD for PrEP in men/TGW who have sex with men and are at-risk of HIV-1 infection.	The primary efficacy endpoint was the rate of HIV-1 infection in MSM/TGW who were administered daily F/TAF or F/TDF with a minimum follow-up of 48 weeks and at least 50% of subjects had 96 weeks of follow-up after randomization.	The total duration is 96 weeks.	F/TAF QD (n=2694) F/TDF QD (n=2693)	MSM /TGW

2.2 Data Sources

NDA 208,215 / S12 contains the efficacy and safety results for subjects in Study GS-US-412-2055. This reviewer conducted primary efficacy analyses to verify the Applicant's results.

1. Reviewed protocols, statistical analysis plans, efficacy results and conclusions in the following submitted documents entitled "Statistics Section":
    - Module 1- labeling materials
    - Module 2- 2.5 Clinical Overview and 2.7.3 Summary of Clinical Efficacy
    - Module 5- Clinical Study Reports (CSRs) of the Phase 3 Study GS-US-412-2055

2. Converted SAS transportable files '*.xpt' in \analysis\adam\datasets subfolder as analysis datasets, some of the raw datasets in \tabulations\sdtm subfolder into SAS data files for verification based on the definitions in 'define.xml', 'acrf.pdf', and SAP in the clinical study report (CSR). These files are under CDER Electronic Document Room (EDR) directory of

    \\CDSESUB1\evsprod\NDA208215\0098\m5\datasets\gs-us-412-2055

3. STATISTICAL EVALUATION

Study GS-US-412-2055 will be reviewed and reported in the following sections. All tables and figures were prepared by the statistical reviewer unless otherwise stated.

3.1 Data and Analysis Quality

Overall, the reviewer reproduced primary efficacy analysis findings based on dataset, ADEFF.

The reviewer guides, SAPs and the SAS programs submitted were useful and assisted in an efficient review.

3.2 Evaluation of Efficacy

3.2.1 Study Design of GS-US-412-2055 (DISCOVER) and Endpoints

Note that the summary in Section 3.2.1 is either directly taken from the sponsor's NDA or previous IND submissions, or paraphrased, unless otherwise specified.

Title: A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are at Risk of HIV-1 Infection.

A total of 5000 subjects were planned to be enrolled to receive blinded study drug for 96 weeks, although there were 5399 subjects enrolled in total. Subjects were randomized in a 1:1 ratio to either receive F/TAF or F/TDF (Figure 1). With the assumption of a noninferiority margin of 1.62 and a HIV-1 infection rate of 1.44 per 100 person-years (PY) for both arms (please see "Key statistical issue: The NI margin" section-1 for details), a sample size of 2500 subjects in each arm was expected to provide at least 82% power to show noninferiority of F/TAF to F/TDF.

After randomization, subjects were seen in follow-up visits at Weeks 4, 12, and every 12 weeks thereafter. At each study visit, subjects had the following procedures: HIV tests performed via central laboratory or local laboratory; drug dispensation and adherence and risk reduction counseling; and other assessments.

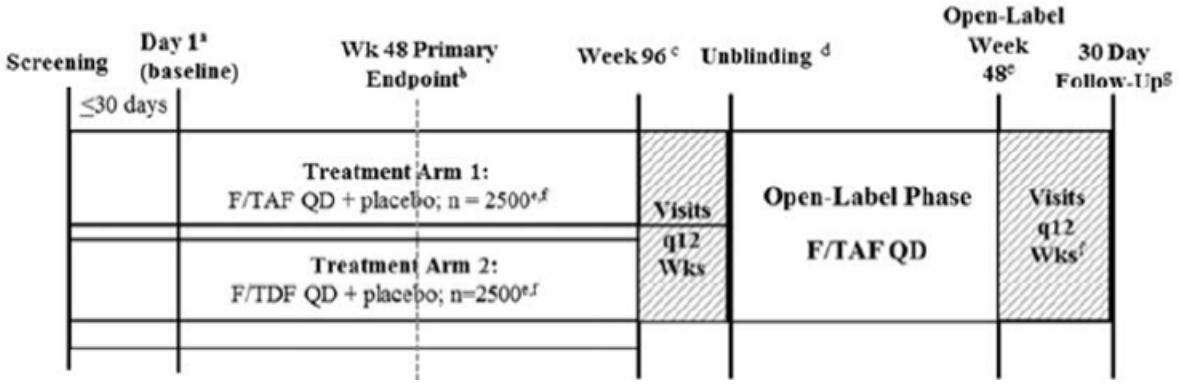

Figure 1: Study Diagram of GS-US-412-2055
(Source: Protocol)

Treatment Arms:

- Treatment Group 1: FDC of emtricitabine 200 mg / tenofovir alafenamide 25 mg(F/TAF) + Placebo-to-match FDC of emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (F/TDF), administered orally once daily (n=2500)
- Treatment Group 2: FDC of emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (F/TDF) + Placebo-to-match FDC of emtricitabine 200 mg / tenofovir alafenamide 25 mg (F/TAF), administered orally once daily (n=2500)

Two sub-studies were conducted based on tenofovir diphosphate (TFV-DP) concentrations in red blood cells from dried blood spot (DBS) samples, an indicator of long-term adherence:

1) a cohort sub-study of approximately 10% of subjects randomly pre-selected to estimate overall rate of adherence, and
2) a case-control sub-study consisting of all subjects who became HIV-infected during the trial matched to 5 randomly selected control subjects (matched by treatment, time, location, and risk behavior) to assess the association between adherence and efficacy.

Statistical Hypothesis for the Primary Efficacy Endpoint:

- **Null hypothesis:** The HIV infection rate ratio of F/TAF over F/TDF is at least 1.62 or higher.
- **Alternative hypothesis:** The HIV infection rate ratio of F/TAF over F/TDF is less than 1.62.

Primary Endpoint: The rate of HIV-1 infection in MSM/TGW who were administered daily F/TAF or F/TDF with a minimum follow-up of 48 weeks and at least 50% of subjects have 96 weeks of follow-up after randomization.

The primary analysis was conducted after all subjects had a minimum follow-up of 48 weeks and at least 50% of the subjects had 96 weeks of follow-up after randomization or prematurely discontinued from the study. The analysis assessed the noninferiority of treatment with F/TAF relative to treatment with F/TDF based on HIV infection rate ratio estimation from a Poisson

regression model. Noninferiority was assessed using a 95% CI constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect and a noninferiority margin of 1.62.

An external multidisciplinary Independent Data Monitoring Committee (IDMC) reviewed the progress of the study and performed interim reviews of the safety data to protect subject welfare and preserve study integrity. There were three interim analysis performed for the IDMCs after 50% of subjects reached Weeks 24, 48 and 72, respectively, an alpha of 0.00001 was spent. Therefore, the significance level for the 2-sided test in the primary analysis was 0.04997 (corresponding to 95.003% CI).

No formal interim efficacy analysis, which may have led to early termination for efficacy or futility, was planned.

Duration of at risk of HIV infection was defined as the time between Day 1 (first dose date) and the end date (end date – Day 1 date +1), where end date was defined as the last at-risk of HIV infection date:

- For subjects who had been diagnosed as infected with HIV: the date of HIV infection diagnosis

- For subjects who had not been infected with HIV: the date of the last post-baseline HIV laboratory test (either local HIV or Covance HIV laboratory tests, including the 30-day follow-up visit)

In the person-year (PY) calculation, a year is 365.25 days.

HIV-1 infection was defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab:

1) Serologic evidence of seroconversion (reactive screening HIV Antigen/Antibody or Antibody test, confirmed by reactive HIV-1/HIV-2 differentiation assay), or

2) Virologic evidence of HIV-1 infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV-1 RNA test), or

3) Evidence of acute HIV-1 infection (reactive p24 Antigen or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Antibody results)

The date of HIV infection diagnosis was assessed by a retrospective look, starting from the date of the first positive virologic evidence, through the preceding test results from other contributing HIV tests (including both Covance and local tests). The look back stops at the first date with negative assessments on all available HIV tests prior to the date of first positive virologic evidence. The date of HIV-1 diagnosis is set at the earliest positive result in the retrospective look process from either an on-site rapid test, a test sent to the central Covance

laboratory, or any other provided local test performed outside of the study that documents the presence of HIV infection.

In the SAP, the Applicant specified **six safety endpoints** with a fallback procedure in the sequential order given below with pre-specified 2-sided alpha levels:

a) Hip bone mineral density (BMD) (alpha spent =0.02)
b) Spine BMD (alpha spent =0.01)
c) Urine beta-2-microglobulin to creatinine ratio (alpha spent =0.02)
d) Urine retinol binding protein (RBP) to creatinine ration (alpha spent =0.00)
e) Distribution of urine protein (UP) and urine protein-to-creatinine ratio (UPCR) categories (alpha spent = 0.00)
f) Serum creatinine (alpha spent = 0.00)

Comments: This review will not cover these safety endpoints. Please see clinical review for more details regarding any clinical relevance of these analysis results.

Populations for Analyses:

- **Safety analysis set (Safety):** included all subjects who were randomized and have received at least 1 dose of study drug.

  Safety analysis set was the primary analysis set for safety analyses. Subjects were grouped according to the treatment received.

- **Full analysis set (FAS):** included all subjects who

  1) were randomized into the study,
  2) had received at least 1 dose of study drug,
  3) were not HIV positive on Day 1 which defined as subjects with either:
     a) negative Covance antibody test results at first post baseline assessment or
     b) negative local lab Day 1 rapid test, and
  4) had at least one post-baseline HIV laboratory assessment (from either local or central laboratory). Negative Covance antibody test results are defined as either:
     a) a negative HIV Screening antibody test result or
     b) a positive Screening antibody test plus a negative discrimination antibody test result.

  Subjects were grouped according to the treatment to which they were randomized. The FAS was the primary analysis set for the efficacy analyses.

- **Per Protocol analysis set (PP):** consisted of all subjects in the FAS excluding those with any of the major protocol violations, such as pre-existing HIV infection, vaccinated for HIV, or subjects who meet exclusion criterion, etc. Subjects was grouped according to

the treatment they received. The PP analysis set was used for an on-study drug PrEP treatment (on-treatment) HIV infection sensitivity analyses of the primary endpoint.

Analysis Windows:

- **Study Day 1** is defined as the day when the first dose of study drug (i.e., F/TAF or Placebo-to-match F/TAF, F/TDF or Placebo -to-match F/TDF) was taken, as recorded on the Study Drug Administration eCRF form.

- **Study Days** are calculated relative to Study Day 1. For events that occurred on or after the Study Day 1 date, the number of study days is calculated as (visit date minus Study Day 1 date plus 1). For events that occurred prior to Study Day 1, the number of study days is calculated as (visit date minus Study Day 1 date).

- **Last Study Date** is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for subjects who prematurely discontinued study or who completed study according to the Study Completion eCRF.

- **Last At-Risk of HIV Infection Date** is

    1) the date of HIV infection diagnosis as defined above for subjects who have been diagnosed as infected with HIV or

    2) the date of the last post-baseline HIV laboratory test (either local rapid or Covance HIV laboratory tests, including the 30-day follow-up visit date) for subjects who have not been infected with HIV.

- **Duration of at risk of HIV infection** is defined as the time between Day 1 (first dose date) and the end date (end date – Day 1 date +1), where end date is defined as the last at-risk of HIV infection date. A year is 365.25 days.

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. The analysis windows are listed in Table 3 below.

Table 3 Analysis Windows for HIV, Hematology, Chemistry, Urinalysis, Renal Biomarkers, eGFRCG, Vital Signs, Weight, CASI Follow-Up Questionnaire, and DBS

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week K (K is every 12 weeks after previous visit)	K*7	(K-6)*7+1	(K+6)*7

HIV laboratory tests include both Covance central laboratory tests (HIV antibody screening tests, HIV Antibody Supplemental tests, qualitative and quantitative tests) and local laboratory tests (rapid HIV-1 Ag/Ab test or other local laboratory tests collected from eCRFs).
CASI follow-up questionnaire collected at post-baseline visits only, no baseline analysis window will be applied.
Source: Table 3-1 in the SAP

From now on, DVY and TVD are used instead of F/TAF and F/TDF in order to be consistent with the CSR.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.1 Disposition

The statistical reviewer reproduced the Applicant's disposition results in safety population for the study.

Screening for the trial began in September 2016 and full enrollment was completed in June 2017. Of 5857 subjects from 94 study sites in North America and the European Union (EU) screened, 364 failed screening, of which 49 were HIV positive at screening. As a result, a total of 5399 subjects were randomized, and only 5387 subjects received study drug (2694 in DVY arm and 2693 in TVD arm). These 5387 subjects consist of safety analysis set**.**

Of note, in the ADSL dataset submitted for the trial, there were 5895 records, with 5890 subjects with SCRNFL='Y' instead of 5857 subjects as stated in the clinical study report (CSR), 5400 subjects with RANDFL='Y' instead of 5399 subjects as stated in the CSR (2700 subjects randomized in the TVD arm instead of 2699 as stated in the CSR). According to the Applicant, the discrepancies were due to the limited number of individuals who did not meet enrollment criteria and were re-screened by the investigator. For the screened population, all screening records were captured in the ADSL dataset. Therefore, if a subject was screened twice, two

separate records were created in the ADSL dataset. In contrast, the CSR only presented the "unique" number of screened subjects based on date of birth, race, ethnicity, sex, country, and initials among subjects with screening visits.

The difference between 5890 subjects with SCRNFL='Y' in the ADSL dataset and 5857 subjects in the CSR is 33. Thirty-one subjects were screen failures at the first screening visit, but met enrollment criteria and were randomized at the second screening visit. One subject ([redacted] and [redacted]) was screened and failed twice. The remaining one subject was screened and randomized twice by mistake, which led to the one subject difference in the randomized population TVD arm (2700 subjects in the ADSL dataset vs. 2699 subjects in the CSR):

- Subject ID "[redacted] – randomized in error
- Subject ID "[redacted]" – confirmed by the clinical site to be the correct Subject ID continuing in the study

Comments: The number of subjects in the safety and FAS analysis sets match with the CSR.

Among 5387 subjects in the safety analysis set (DVY 2694, TVD 2693), 83.6% (4505 subjects; DVY 83.2%, 2242 subjects; TVD 84.0%, 2263 subjects) were continuing study drug, and 85.8% (4623 subjects) were continuing in the study off study drug at the time of the primary analysis data cut date (Table 4 below). Overall, 16.4% (882 subjects) of the randomized and treated subjects prematurely discontinued study drug prior to the primary analysis data cut date. The proportions of subjects continuing study drug were evenly distributed across the 2 treatment arms. Only 0.4% (22 subjects) prematurely discontinued study drug due to HIV-1 infection.

Table 4: Subjects Disposition for study GS-US-412-2055 (Safety)

	DVY	TVD	Total
Total	2694	2693	5387
Continuing study Drug			
Y	2242(83.2%)	2263(84.0%)	4505(83.6%)
N	452(16.8%)	430(16.0%)	882(16.4%)
Reasons of prematurely stopped Study Drug			
Death	1(0.2%)	2(0.5%)	3(0.3%)
HIV-1 Infection	4(0.9%)	9(2.1%)	13(1.5%)
Adverse Event	36(8.0%)	49(11.4%)	85(9.6%)
Lost to Follow-Up	201(44.5%)	170(39.5%)	371(42.1%)
Investigator's Discretion	5(1.1%)	10(2.3%)	15(1.7%)
Non-Compliance with Study Drug	8(1.8%)	12(2.8%)	20(2.3%)
Protocol Violation	4(0.9%)	3(0.7%)	7(0.8%)
Subject Decision	193(42.7%)	175(40.7%)	368(41.7%)
Reasons of prematurely stopped Study Drug of HIV-1 infected subjects			
n	7	15	22
HIV-1 Infection	4(57.1%)	9(60.0%)	13(59.1%)
Adverse Event	1(14.3%)	2(13.3%)	3(13.6%)

Non-Compliance with Study Drug	(%)	2(13.3%)	2(9.1%)
Subject Decision	2(28.6%)	2(13.3%)	4(18.2%)

Among 5387 subjects in the safety analysis set, 52 subjects (DVY 24, TVD 28) did not have any post-baseline HIV laboratory assessment and were excluded from the full analysis set (FAS). As a result, FAS consists of 5335 subjects (DVY 2670, TVD 2665) for the primary efficacy analyses.

3.2.2.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics were generally similar between the 2 treatment arms (**Table 13** in Appendix). The median age of subjects was 34 years (range, 18-76); 84% were White, 9% Black/Mixed Black, 4% Asian, and 24% Hispanic/Latino. Only 1% (74 subjects) were TGW and 99% of subjects were MSM. The highest educational level attained by 57% of the population was 4 years of college or higher. Seventy-one percent of subjects (71%) were employed full-time. Sixty percent of subjects (60%) were in the U.S.

At baseline, 905 subjects (17%) reported receiving TRUVADA for PrEP. Sixty-one percent of subjects (61%) reported that they did not use a condom frequently to manage the risk of getting HIV, and 74% of subjects did not ask their partner to use a condom for anal sex to manage the risk of getting HIV. Fifty-six percent of subjects (56.0%) were circumcised. Fifty-nine percent of subjects (59%) reported via the CASI questionnaire having 3 or more unprotected receptive anal sex intercourse (URAI) partners in the 90 days prior to screening. Forty-four percent of subjects (44%) reported having 3 or more unprotected insertive anal intercourse (UIAI) partners in the 90 days prior to screening.

3.2.3 Statistical Methodologies

Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter). For rate ratio, the Applicant used a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect to construct its 95.003% CI. The reviewer used PROC Poisson in StatXact PROC to verify the CIs.

3.2.4 Results and Conclusions

3.2.4.1 Summary of Applicant's Results

In the FAS, there were a total 22 subjects infected during the study, 7 in DVY arm and 15 in TVD arm. The rate ratio for the HIV incidence rate (DVY vs TVD) was 0.468 (95.003% CI: 0.191, 1.149) (**Table 5**). DVY was demonstrated to be noninferior to TVD, as the upper bound of the 2-sided 95.003% CI of the rate ratio (1.149) was less than 1.62.

Comments: Of note, the Applicant did present rate difference analysis results as the secondary analysis in the table. This analysis was deemed by this reviewer to not be appropriate for this case.

Table 5: Applicant's HIV-1 Infection Rates Results for Study GS-US-412-2055 (FAS)

Table 18. GS-US-420-2055: HIV Incidence Rates While at Risk of HIV Infection (Rate Ratio and Rate Difference Methods) (Full Analysis Set)

	DVY (N = 2670)	TVD (N = 2665)	DVY vs. TVD (95.003% CI)
Person-years of Follow-Up	4369.7	4386.2	—
Number of HIV Infection Events	7	15	—
HIV Infection Rate per 100 Person-years	0.160	0.342	—
95% Exact CI	0.064, 0.330	0.191, 0.564	—
Rate Ratio (Primary Analysis)[a]	0.468		0.191, 1.149
Rate Difference[b]	−0.182		−0.424, 0.045

a Noninferiority margin 1.62
b Noninferiority margin 1.2 per 100 PY
HIV infection based on serologic evidence (excluding HIV vaccinated participants), virologic evidence, and/or evidence of acute infection.
Person-years is the summation of all participants' total number of years (year=365.25 days) of follow-up in study between the first dose date and either 1) date of HIV diagnosis for participants with HIV or 2) date of last post-baseline HIV laboratory test (incl. 30-day follow-up visit and either local or Covance labs) for participants not infected with HIV.
95.003% CI of HIV infection rate ratio from a generalized model with a Poisson distribution and logarithmic link with treatment as main effect.
Hybrid 95.003% exact CI for HIV infection rate difference of F/TAF - F/TDF based on the single Poisson rate parameter approach (Li 2011, Ulm 1990).
95% exact CI was based on the single Poisson rate parameter method (Ulm 1990).

Source: study GS-US-412-2055 CSR, Table 18.

The Applicant did a sensitivity analysis as 5 out of 22 infected subjects did not have post-baseline HIV-1 laboratory assessment before infection were detected. These 5 subjects (1 in DVY and 4 in TVD) were called suspected baseline infection. If these 5 subjects were excluded from the primary efficacy analysis:

- DVY: 6 subjects; 0.138 infections per 100 PY of follow-up (95% exact CI: 0.050, 0. 299)
- TVD: 11 subjects; 0.252 infections per 100 PY of follow-up (95% exact CI: 0.126, 0.450)

DVY was demonstrated to be noninferior to TVD, as the upper bound of the 2-sided 95.003% CI of the rate ratio (0.547 [95.003% CI: 0.202, **1.479**]) was less than 1.62.

The forest plot of selected subgroup analysis of HIV incidence rate ratio is shown in Figure 2 below. Only subgroups of age < 25 years and Ex-US had incidence rate ratios larger than 1 in terms of the point estimate, however, the 95% CIs still covered 1. Analyses comparing HIV infection rates between the DVY and TVD groups within prespecified subgroups showed that DVY and TVD were similar for use as PrEP in all prespecified subgroups, as the 2-sided 95% exact CIs for the HIV-1 infection rates overlapped between the 2 treatment arms.

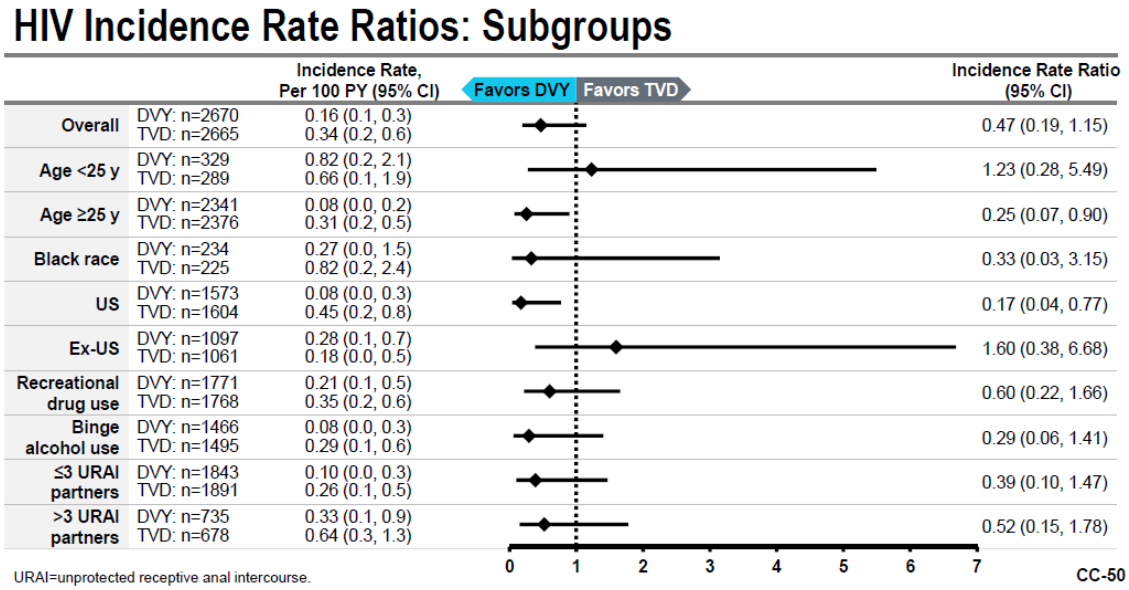

Figure 2: Forest Plot of Subgroup Analyses of HIV Incidence Rate Ratio of GS-US-412-2055 (Source: AC slides from the Applicant)

The Applicant summarized epidemiology data and showed that use of DVY or TVD for PrEP was more effective for preventing HIV-1 infection than not using PrEP, as the upper limits of the 95% exact CIs for the HIV-1 incidence rates in subjects using DVY or TVD for PrEP in this study were below the lower limit of the 95% CI for the HIV-1 infection rate in MSM not using PrEP across 25 US MSAs overlapping with Study GS-US-412-2055 sites, which was 4.02 per 100 PY with 95% CI of [3.56, 3.66].

Comments: Of note, the reviewer cannot verify these epidemiology data results.

3.2.4.2 Study Primary Efficacy Results

➢ **Primary Efficacy Analysis Results**

The reviewer replicated the Applicant's primary efficacy endpoint results (Table 6). DVY was demonstrated to be noninferior to TVD, as the upper bound of the 2-sided 95.003% CI of the rate ratio (1.149) was less than 1.62.

Table 6: Primary Efficacy Analysis HIV-1 Infection Rates for Study GS-US-412-2055 (FAS)

		DVY (N=2670)	**TVD (N=2665)**	**Ratio of DVY / TVD (95.003% CI)**
Person-years of Follow-Up		4369.7	4386.2	
Number of HIV-1 Infected Events		7	15	
HIV-1 Infection Rate per 100 PYs		**0.160**	**0.342**	
Sponsor used	95% Exact CI[a]	(0.064, 0.330)	(0.191, 0.564)	
	Rate Ratio	**0.468**		(0.191, **1.149**)[b]
95% exact CI of a Poisson Rate[c]		(0.06, 0.33)	(0.19, 0.56)	

a: Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
b: 95.003% CI was constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect.
c: Using PROC Poisson in StatXact PROC.

There were 5 out of 22 infected subjects who did not have a post-baseline HIV-1 laboratory assessment before infection was detected. These 5 subjects (1 in DVY and 4 in TVD) were labeled as suspected baseline infection. Four subjects were infected within approximately 4 weeks of treatment and one subject was on treatment for about 12 weeks (**Table 7**).

The rate ratio changed from 0.468 to 0.547 and its 95.003% CI was [0.202, **1.481**] (**Table 8**), which is the same as the Applicant's results in the CSR, but the overall conclusion remained the same.

Table 7: Study Drug Duration of 5 Subjects Who were Suspected to Have Baseline Infection for Study GS-US-412-2055 (FAS)

Usubjid*	Treatment Received	Follow-up in years	Number of Days Infection Detected
(b) (6)	TVD	0.0794	29
	TVD	0.2327	85
	TVD	0.0794	29
	DVY	0.0794	29
	TVD	0.0986	36

*: unique subject ID.

Table 8: Sensitivity Analysis HIV-1 Infection Rates Excluding 5 Subjects Who were Suspected to Have Baseline Infection for Study GS-US-412-2055 (FAS)

		DVY (N=2669)	**TVD (N=2661)**	**Ratio of DVY / TVD (95.003% CI)**
Person-years of Follow-Up		4369.6	4385.7	
Number of HIV-1 Infected Events		6	11	
HIV-1 Infection Rate per 100 PY		**0.137**	**0.251**	
Sponsor used	95% Exact CI[a]	(0.050, 0.299)	(0.125, 0.449)	
	Rate Ratio	**0.547**		(0.202, **1.481**)[b]
95% exact CI of a Poisson Rate[c]		(0.05, 0.30)	(0.13, 0.45)	

a: Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
b: 95.003% CI was constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect.
c: Using PROC Poisson in StatXact PROC.

- **Other Sensitivity Efficacy Analysis Results**

First, there were 52 subjects who were in the safety analysis set and excluded from the FAS because they did not have any post-baseline HIV-1 laboratory assessment. The treatment duration for these 52 subjects are listed in **Table 9**. If subjects with at least 14 days of treatment were not excluded from the FAS, a total of 15 subjects (9 in DVY and 6 in TVD) will be added back to FAS for efficacy analysis. If assuming all these 15 subjects were infected as the worst scenario, the analysis results are listed in **Table 10** below. The rate ratio changed from 0.468 to 0.765 and its 95.003% CI was [0.399, **1.466**]. The conclusion remained unchanged.

Table 9: Study Drug Duration of 52 Subjects Who were Excluded from FAS

Arm	Treatment Duration (in days)					Total
	1	2 – 6	7 - 13	14 – 20	21- 35	
DVY	10	3	2	3	6	24
TVD	16	2	4	4	2	28
total	26	5	6	7	8	52

Table 10: Sensitivity Analysis HIV-1 Infection Rates including 15 Subjects Who were Excluded from FAS for Study GS-US-412-2055

		DVY (N=2669)	**TVD (N=2661)**	**Ratio of DVY / TVD (95.003% CI)**
Person-years of Follow-Up		4370.4	4386.7	
Number of HIV-1 Infected Events		16	21	
HIV-1 Infection Rate per 100 Person-years		**0.366**	**0.479**	
Sponsor used	95% Exact CI[a]	(0.209, 0.595)	(0.296, 0.732)	
	Rate Ratio	**0.765**		(0.399, **1.466**)[b]
95% exact CI of a Poisson Rate[c]		(0.21, 0.59)	(0.30, 0.73)	

a: Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
b: 95.003% CI was constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect.
c: Using PROC Poisson in StatXact PROC.

Second, the reviewer explored the number of infected subjects in the DVY arm that would be needed to fail to demonstrate NI if the number of infection events in the TVD arm remained consistent at 15. As shown in **Table 11** below, when there were 12 infected subjects in the DVY arm, the rate ratio changed from 0.468 to 0.803 and its 95.003% CI was [0.376, **1.716**]. DVY would fail to demonstrate that DVY was noninferior to TVD, as the upper bound of the 2-sided 95.003% CI of the rate ratio (1.716) was greater than 1.62.

Table 11: Sensitivity Analysis HIV-1 Infection Rates with Different Number of Subjects Infected in DVY Arm for Study GS-US-412-2055 (FAS)

Case	DVY			TVD			**Ratio of DVY / TVD (95.003% CI)**
	PY	Infected	Infection rate (95% CI)	PY	Infected	Infection rate (95% CI)	
1	4369.7	7	0.160 (0.064, 0.330)	4386.2	15	0.342 (0.191, 0.564)	0.468 (0.191, 1.149)
2		8	0.183 (0.079, 0.361)				0.535 (0.227, **1.263**)
3		9	0.206 (0.094, 0.391)				0.602 (0.264, 1.376)
4		10	0.229 (0.110, 0.421)				0.669 (0.301, 1.490)
5		**11**	0.252 (0.126, 0.450)				0.736 (0.338, **1.603**)
6		**12**	0.275 (0.142, 0.480)				0.803 (0.376, **1.716**)
7		13	0.300 (0.158, 0.509)				0.870 (0.414, **1.828**)

- **Adherence Rate by Pill Count**

There are two assumptions used in the calculation of adherence rate by pill count:

- If return is missing, assume return=0;
- Last dispense w/o returned data, assume all pills taken as scheduled;

The adherence rate=(pill count dispensed – pill count returned)/total pill count supposed to take.

The median of overall adherence rate was 97.9% (**Table 12**). The median of adherence rate among infected subjects (94.5%) was slightly lower than that among uninfected subjects (97.9%). This difference was mainly due to the difference in adherence rates between infected vs. uninfected subjects within TVD arm.

Table 12: Study Drug Adherence Rate by Pill Count (Safety)

	Infected	Uninfected	Total
N	22	5313	5335
Adherence Rate (Pill Count) -- Overall			
Mean (SE)	85.77 (4.244)	93.62 (0.179)	93.59 (0.179)
Median	**94.51**	**97.90**	97.89
Range	(32.05, 100.0)	(0.17, 100.0)	(0.17, 100.0)
STD	19.90	13.02	13.06
Adherence Rate Category (Pill Count) -- Overall			
< 30%	(%)	78(1.5%)	78(1.5%)
>=30 to <60%	3(13.6%)	71(1.3%)	74(1.4%)
>=60 to <80%	3(13.6%)	220(4.1%)	223(4.2%)
>=80 to <90%	2(9.1%)	493(9.3%)	495(9.3%)
>=90 to <95%	4(18.2%)	822(15.5%)	826(15.5%)
>= 95%	10(45.5%)	3629(68.3%)	3639(68.2%)
	Infected	Uninfected	Total
DVY only (N)	**7**	**2663**	**2670**
Adherence Rate (Pill Count) -- DVY only			
Mean (SE)	87.96 (9.385)	93.39 (0.259)	93.38 (0.260)
Median	**97.56**	**97.89**	97.88
Range	(32.05, 100.0)	(0.67, 100.0)	(0.67, 100.0)
STD	24.83	13.37	13.41
Adherence Rate Category (Pill Count) -- DVY only			
< 30%	(%)	42(1.6%)	42(1.6%)
>=30 to <60%	1(14.3%)	39(1.5%)	40(1.5%)
>=60 to <80%	(%)	116(4.4%)	116(4.3%)
>=80 to <90%	(%)	262(9.8%)	262(9.8%)
>=90 to <95%	2(28.6%)	399(15.0%)	401(15.0%)
>= 95%	4(57.1%)	1805(67.8%)	1809(67.8%)
TVD only (N)	**15**	**2650**	**2665**
Adherence Rate (Pill Count) -- TVD only			

Mean (SE)	84.74 (4.666)	93.85 (0.246)	93.80 (0.246)
Median	**93.70**	**97.92**	97.91
Range	(43.82, 100.0)	(0.17, 100.0)	(0.17, 100.0)
STD	18.07	12.65	12.70
Adherence Rate Category (Pill Count) -- TVD only			
< 30%	(%)	36(1.4%)	36(1.4%)
>=30 to <60%	2(13.3%)	32(1.2%)	34(1.3%)
>=60 to <80%	3(20.0%)	104(3.9%)	107(4.0%)
>=80 to <90%	2(13.3%)	231(8.7%)	233(8.7%)
>=90 to <95%	2(13.3%)	423(16.0%)	425(15.9%)
>= 95%	6(40.0%)	1824(68.8%)	1830(68.7%)

Comments: The reviewer did not conduct independent analysis of TFV-DP level in red blood cells.

According to the CSR, most subjects in both groups had TFV-DP levels in red blood cells consistent with high adherence (≥ 4 days of dosing per week) in the DBS substudy. Other objective adherence measure, such as TFV and FTC levels in plasma and TFV-DP and FTC-TP levels measured in PBMCs at Week 4, confirmed the high adherence results from the DBS substudy. The estimated high adherence rates likely explain the low numbers of HIV seroconversions observed in this trial.

3.3 Evaluation of Safety

See the clinical review for the evaluation of safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Note that subgroup analyses need to be interpreted with caution because they were post-hoc (with the exception of gender, race, age and geographic region), with no multiple comparison adjustments small sample sizes within subgroups, and small number of subjects who were infected.

4.1 Gender, Race, Age, and Geographic Region

The subgroup analysis for these covariates were conducted, and none had significant impact on the infection rate as the 2-sided 95% CI for the HIV-1 infection rates in DVY and TVD arms overlapped (**Table 14** in appendix).

4.2 Other Special/Subgroup Populations

The subgroup analysis for other baseline covariates were conducted, and none had significant impact on the infection rate as the 2-sided 95% CI for the HIV-1 infection rates in DVY and TVD arms overlapped (**Table 14** in appendix).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Among 5335 subjects in the FAS, 22 subjects (0.4%) were infected with HIV-1 during the trial, and of which, 7 were in the DVY arm and 15 were in the TVD arm. The HIV-1 infection rates were 0.160 per 100 PY and 0.342 per 100 PY in DVY arm and TVD arm respectively. The upper bound of 95.003% CI of ratio of DVY vs. TVD was 1.149, which is lower than pre-specified NI margin of 1.62. Therefore, the trial demonstrated that DVY was non-inferior to TVD in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population.

Sensitivity analyses, by excluding the 5 suspected baseline infected subjects and including 15 additional subjects (9 in DVY and 6 in TVD) who were excluded from FAS due to lack of post-baseline HIV laboratory assessment, also demonstrated that DVY was non-inferior to TVD in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population.

The Applicant summarized the 2016 CDC infection data in non-study PrEP-eligible MSM at risk of HIV-1 in 25 US metropolitan statistical areas (MSAs), which are overlapping with GS-US-412-2055 sites, as supportive. The infection rate was 4.02 per 100 PY with 95% CI of [**3.56**, 3.66]. The upper limits of the 95% exact CIs for the HIV-1 incidence rates in subjects using DVY or TVD for PrEP in this study were below the lower limit of the 95% CI for the HIV-1 infection rate in MSM not using PrEP across 25 US MSAs overlapping with Study GS-US-412-2055 sites.

Overall, the reviewer concluded that the trial demonstrated non-inferiority of DVY to TVD in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population. There was no other statistical issue identified.

5.2 Conclusions and Recommendations

The trial demonstrated that DVY was non-inferior to TVD in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population.

The Applicant proposed to extrapolate the treatment effect to cis-gender women for a possible broad indication. However, there are no data to support the indication to cis-gender women based on the data reviewed. Please see the clinical review for more details regarding the discussion on the indication to all adults including cis-gender women and adolescents.

5.3 Labeling Recommendations

The final efficacy table for study GS-US-412-2055 in the label is as follows:

HIV-1 Infection Results in DISCOVER Trial – Full Analysis Set

	DESCOVY (N=2,670)	TRUVADA (N=2,665)	Rate Ratio (95% CI)
	4,370 person-years	4,386 person-years	
HIV-1 infections n (%)	7	15	
Rate of HIV-1 infections per 100 person-years	0.16	0.34	0.468 (0.19, 1.15)

CI = Confidence interval.

There will be limitations of use associated with the indication. Please see the clinical review for details.

APPENDICES

Table 13: Demographics and Baseline Characteristics for Study GS-US-412-2055 (Safety)

	DVY	TVD	Total
Treated (Safety)			
N	2694	2693	5387
Men Who Have Sex with			
MSM	2649(98.3%)	2664(98.9%)	5313(98.6%)
TGW	45(1.7%)	29(1.1%)	74(1.4%)
Race			
AMERICAN INDIAN OR ALASKA NATIVE	12(0.4%)	14(0.5%)	26(0.5%)
ASIAN	113(4.2%)	120(4.5%)	233(4.3%)
BLACK OR AFRICAN	222(8.2%)	216(8.0%)	438(8.1%)
NATIVE HAWAIIAN OR PACIFIC ISLANDER	17(0.6%)	23(0.9%)	40(0.7%)
WHITE	2264(84.0%)	2247(83.4%)	4511(83.7%)
OTHER	63(2.3%)	68(2.5%)	131(2.4%)
NOT PERMITTED	3(0.1%)	5(0.2%)	8(0.1%)
Race Category 1			
Black	240(8.9%)	234(8.7%)	474(8.8%)
Non-Black	2451(91.1%)	2454(91.3%)	4905(91.2%)
Ethnicity			
HISPANIC OR LATINO	635(23.6%)	683(25.4%)	1318(24.5%)
NOT HISPANIC OR LATINO	2058(76.4%)	2008(74.6%)	4066(75.5%)
NOT PERMITTED	1(0.0%)	2(0.1%)	3(0.1%)
Age (Year)			
Mean (SE)	35.97 (0.204)	36.42 (0.207)	36.19 (0.145)
Median	34.00	34.00	34.00
Range	(18.00, 76.00)	(18.00, 72.00)	(18.00, 76.00)
STD	10.56	10.73	10.65
Age Category 1 (25yrs)			
< 25	336(12.5%)	293(10.9%)	629(11.7%)
>= 25	2358(87.5%)	2400(89.1%)	4758(88.3%)
Age Category 2 (25, 50, 65yrs)			
< 25	336(12.5%)	293(10.9%)	629(11.7%)
>=25 to <50	2028(75.3%)	2014(74.8%)	4042(75.0%)
>=50 to <65	297(11.0%)	350(13.0%)	647(12.0%)
>=65	33(1.2%)	36(1.3%)	69(1.3%)
Baseline Weight (kg)			
Mean (SE)	83.48 (0.338)	82.75 (0.323)	83.12 (0.234)
Median	80.70	80.00	80.30
Range	(45.80, 188.3)	(45.20, 179.7)	(45.20, 188.3)
STD	17.56	16.77	17.17

Baseline Height (cm)			
Mean (SE)	178.0 (0.144)	177.7 (0.144)	177.8 (0.102)
Median	178.0	177.8	177.8
Range	(139.7, 203.2)	(142.2, 203.2)	(139.7, 203.2)
STD	7.498	7.498	7.499
Baseline BMI (kg/m^2)			
Mean (SE)	26.31 (0.097)	26.20 (0.096)	26.26 (0.068)
Median	25.28	25.31	25.31
Range	(15.95, 53.09)	(16.58, 61.83)	(15.95, 61.83)
STD	5.013	4.982	4.997
Baseline BMI Category 1 (kg/m^2)			
<=25	1260(46.8%)	1260(46.8%)	2520(46.8%)
25<=, <30	952(35.3%)	987(36.7%)	1939(36.0%)
>=30	481(17.9%)	446(16.6%)	927(17.2%)
missing	1(0.0%)	(%)	1(0.0%)
Baseline HBV Infection Status			
N	2686(100.0%)	2683(100.0%)	5369(100.0%)
Baseline HCV Infection Status			
N	1916(100.0%)	1892(100.0%)	3808(100.0%)
Any prior Truvada for PrEP			
N	2066(76.7%)	2074(77.0%)	4140(76.9%)
Y	628(23.3%)	619(23.0%)	1247(23.1%)
Took Truvada for PrEP at Baseline			
N	2229(82.7%)	2253(83.7%)	4482(83.2%)
Y	465(17.3%)	440(16.3%)	905(16.8%)
Sexuality			
Bisexual	171(6.4%)	214(8.0%)	385(7.2%)
Gay/Homosexual	2461(91.8%)	2434(90.9%)	4895(91.4%)
Straight/Heterosexual	25(0.9%)	16(0.6%)	41(0.8%)
Other	23(0.9%)	13(0.5%)	36(0.7%)
Highest Education Level			
Less than high school	52(1.9%)	41(1.5%)	93(1.7%)
High school/GED	285(10.6%)	257(9.6%)	542(10.1%)
Some college	479(17.9%)	487(18.2%)	966(18.0%)
2-year college/AA	291(10.9%)	325(12.1%)	616(11.5%)
4-year college	892(33.3%)	880(32.9%)	1772(33.1%)
Master's degree	445(16.6%)	430(16.1%)	875(16.3%)
Doctoral degree	82(3.1%)	96(3.6%)	178(3.3%)
Professional degree	124(4.6%)	129(4.8%)	253(4.7%)
Other	30(1.1%)	32(1.2%)	62(1.2%)
Work Situation			
Full-time employment	1884(70.3%)	1903(71.1%)	3787(70.7%)
Part-time employment	297(11.1%)	280(10.5%)	577(10.8%)
Part/full time student/education/training	193(7.2%)	198(7.4%)	391(7.3%)

Retired	51(1.9%)	48(1.8%)	99(1.8%)
Unemployed	207(7.7%)	210(7.8%)	417(7.8%)
Other	48(1.8%)	38(1.4%)	86(1.6%)
Baseline Hip BMD (g/cm2)			
Mean (SE)	1.03 (0.011)	1.02 (0.010)	1.02 (0.007)
Median	1.01	1.01	1.01
Range	(0.65, 1.66)	(0.70, 1.40)	(0.65, 1.66)
STD	0.154	0.132	0.144
Baseline Spine BMD (g/cm2)			
Mean (SE_	1.13 (0.012)	1.13 (0.010)	1.13 (0.008)
Median	1.13	1.13	1.13
Range	(0.76, 1.70)	(0.78, 1.50)	(0.76, 1.70)
STD	0.161	0.138	0.150
Baseline eGFR (mL/min)			
Mean (SE)	127.9 (0.661)	126.4 (0.661)	127.2 (0.467)
Median	122.9	121.2	121.8
Range	(60.10, 345.3)	(61.50, 391.4)	(60.10, 391.4)
STD	34.30	34.30	34.30
Baseline Serum Creatinine (mg/dL)			
Mean (SE)	0.96 (0.003)	0.96 (0.003)	0.96 (0.002)
Median	0.94	0.94	0.94
Range	(0.58, 1.71)	(0.52, 1.95)	(0.52, 1.95)
STD	0.146	0.148	0.147
Medical History - Rectal Gonorrhea			
N	2420(89.8%)	2431(90.3%)	4851(90.1%)
Y	274(10.2%)	262(9.7%)	536(9.9%)
Baseline Rectal Gonorrhea			
Positive	123(4.6%)	113(4.2%)	236(4.4%)
Indeterminate	9(0.3%)	4(0.1%)	13(0.2%)
Negative	2536(95.1%)	2552(95.6%)	5088(95.3%)
Baseline Urine Gonorrhea			
Detected	17(0.6%)	12(0.5%)	29(0.6%)
Not Detected	2601(99.4%)	2600(99.5%)	5201(99.4%)
Baseline Oral Gonorrhea			
Positive	103(4.5%)	130(5.7%)	233(5.1%)
Indeterminate	5(0.2%)	1(0.0%)	6(0.1%)
Negative	2160(95.2%)	2140(94.2%)	4300(94.7%)
Medical History - Rectal Chlamydia			
N	2352(87.3%)	2360(87.6%)	4712(87.5%)
Y	342(12.7%)	333(12.4%)	675(12.5%)
Baseline Rectal Chlamydia			
Positive	199(7.5%)	189(7.1%)	388(7.3%)
Indeterminate	8(0.3%)	3(0.1%)	11(0.2%)
Negative	2462(92.2%)	2478(92.8%)	4940(92.5%)
Baseline Urine Chlamydia			

Detected	61(2.3%)	54(2.1%)	115(2.2%)
Not Detected	2557(97.7%)	2558(97.9%)	5115(97.8%)
Baseline Oral Chlamydia			
Positive	47(2.1%)	43(1.9%)	90(2.0%)
Indeterminate	1(0.0%)	(%)	1(0.0%)
Negative	2215(97.9%)	2225(98.1%)	4440(98.0%)
Medical History - Syphilis			
N	2463(91.5%)	2430(90.2%)	4893(90.8%)
Y	230(8.5%)	263(9.8%)	493(9.2%)
Baseline Syphilis Diagnosis			
N	2687(99.7%)	2689(99.9%)	5376(99.8%)
Y	7(0.3%)	4(0.1%)	11(0.2%)
RAI Partners in 90 Days Prior to Screening			
Mean (SE)	6.13 (0.175)	6.01 (0.186)	6.07 (0.128)
Median	3.00	3.00	3.00
Range	(0.00, 99.00)	(0.00, 99.00)	(0.00, 99.00)
STD	8.915	9.473	9.197
URAI Partners in 90 Days Prior to Screening			
Mean (SE)	3.59 (0.116)	3.45 (0.121)	3.52 (0.084)
Median	2.00	2.00	2.00
Range	(0.00, 70.00)	(0.00, 99.00)	(0.00, 99.00)
STD	5.937	6.186	6.062
URAI Partners in 90 Days Prior to Screening - Group1			
<=2 URAI	1508(58.0%)	1577(60.7%)	3085(59.3%)
> 2 URAI	1094(42.0%)	1020(39.3%)	2114(40.7%)
IAI Partners in 90 Days Prior to Screening			
Mean (SE)	6.89 (0.191)	6.85 (0.211)	6.87 (0.142)
Median	4.00	3.00	4.00
Range	(0.00, 99.00)	(0.00, 99.00)	(0.00, 99.00)
STD	9.757	10.73	10.25
UIAI Partners in 90 Days Prior to Screening			
Mean (SE)	4.24 (0.132)	4.13 (0.143)	4.18 (0.097)
Median	2.00	2.00	2.00
Range	(0.00, 70.00)	(0.00, 99.00)	(0.00, 99.00)
STD	6.759	7.277	7.022
IRAI Partners in 90 Days Prior to Screening - Group1			
<=2 IRAI	1440(55.3%)	1476(56.8%)	2916(56.1%)
> 2 IRAI	1162(44.7%)	1121(43.2%)	2283(43.9%)
Use Condoms to Manage HIV risk at Screening			
N	1660(61.9%)	1628(60.8%)	3288(61.4%)
Y	1020(38.1%)	1049(39.2%)	2069(38.6%)
Ask Partners to Use Condoms to Manage HIV risk at Screening			
N	1991(74.3%)	1981(74.0%)	3972(74.1%)
Y	689(25.7%)	696(26.0%)	1385(25.9%)

Recreational Drug Usage 3 months prior to screening			
N	895(33.4%)	891(33.3%)	1786(33.3%)
Y	1785(66.6%)	1786(66.7%)	3571(66.7%)
Circumcised (Y/N)			
Y	1485(55.4%)	1513(56.5%)	2998(56.0%)
N	1185(44.2%)	1160(43.3%)	2345(43.8%)
N/A (Post-Operative)	10(0.4%)	4(0.1%)	14(0.3%)
Alcohol Usage at Screening			
Never	254(9.6%)	213(7.9%)	467(8.8%)
Monthly or less	439(16.5%)	470(17.5%)	909(17.0%)
2 to 4 times a month	897(33.8%)	942(35.1%)	1839(34.5%)
2 to 3 times a week	792(29.8%)	792(29.6%)	1584(29.7%)
4 or more times a week	275(10.4%)	263(9.8%)	538(10.1%)
Country			
AUT	35(1.3%)	42(1.6%)	77(1.4%)
CAN	191(7.1%)	162(6.0%)	353(6.6%)
DEU	187(6.9%)	183(6.8%)	370(6.9%)
DNK	98(3.6%)	104(3.9%)	202(3.7%)
ESP	219(8.1%)	195(7.2%)	414(7.7%)
FRA	18(0.7%)	14(0.5%)	32(0.6%)
GBR	247(9.2%)	265(9.8%)	512(9.5%)
IRL	40(1.5%)	38(1.4%)	78(1.4%)
ITA	37(1.4%)	21(0.8%)	58(1.1%)
NLD	31(1.2%)	40(1.5%)	71(1.3%)
USA	1591(59.1%)	1629(60.5%)	3220(59.8%)
Region 1			
Canada	191(7.1%)	162(6.0%)	353(6.6%)
European Union	912(33.9%)	902(33.5%)	1814(33.7%)
US-Midwest	103(3.8%)	97(3.6%)	200(3.7%)
US-Northeast	78(2.9%)	64(2.4%)	142(2.6%)
US-South	591(21.9%)	664(24.7%)	1255(23.3%)
US-West	819(30.4%)	804(29.9%)	1623(30.1%)
Region 2			
Ex-US	1103(40.9%)	1064(39.5%)	2167(40.2%)
US	**1591(59.1%)**	**1629(60.5%)**	**3220(59.8%)**
Region 3			
European Union	912(33.9%)	902(33.5%)	1814(33.7%)
US/Canada	1782(66.1%)	1791(66.5%)	3573(66.3%)

Table 14: The Summary Subgroup Analyses of HIV-1 Infection Rate for Study GS-US-412-2055 (FAS)

Factors	DVY			TVD		
	N (PY)	Infected	Infection rate (95% CI)	N (PY)	Infected	Infection rate (95% CI)
Overall	2670 (4369.7)	7	0.160 (0.064, 0.330)	2665 (4386.2)	15	0.342 (0.191, 0.564)
Age (years)						
<25	329 (489.8)	4	0.817 (0.223, 2.091)	289 (451.5)	3	0.664 (0.137, 1.942)
≥25	2341 (3879.9)	3	0.077 (0.016, 0.226)	2376 (3934.7)	12	0.305 (0.158, 0.533)
Race						
Any Black (Black/Mixed Black)	234 (371.3)	1	0.269 (0.007, 1.501)	225 (364.8)	3	0.822 (0.170, 2.404)
Nonblack	2433 (3996.6)	6	0.150 (0.055, 0.327)	2435 (4012.7)	12	0.299 (0.155, 0.522)
Region - 01						
US	1573 (2598.4)	2	0.077 (0.009, 0.278)	1604 (2688.4)	12	0.446 (0.231, 0.278)
Ex-US	1097 (1771.4)	5	0.282 (0.092, 0.659)	1061 (1697.8)	3	0.177 (0.036, 0.516)
Region - 02						
North America (US/Canada)	1762 (2917.1)	3	0.103 (0.021, 0.301)	1766 (2953.6)	14	0.474 (0.259, 0.795)
European Union	908 (1452.6)	4	0.275 (0.075, 0.705)	899 (1432.6)	**1**	**0.070 (0.002, 0.389)**
Highest Level of Education at Screening (CASI)						
<4 Year College	1123 (1788.8)	5	0.280 (0.091, 0.652)	1121 (1803.5)	9	0.490 (0.228, 0.947)
≥4 Year College	1533 (2557.0)	2	**0.078 (0.009, 0.283)**	1528 (2560.0)	6	0.234 (0.086, 0.510)
Baseline F/TDF used for PrEP						
Yes	459 (770.9)	0	0 (*, 0.479)	438 (727.7)	1	0.137 (0.003, 0.766)
No	2211 (3598.9)	7	0.195 (0.078, 0.401)	2227 (3658.4)	14	0.383 (0.209, 0.642)
Recreational Drug Use in the Last 3 Months Prior to Screening (CASI)						
Yes	1771 (2875.3)	6	0.209 (0.077, 0.454)	1768 (2884.5)	10	0.347 (0.166, 0.638)
No	885 (1470.5)	1	**0.068 (0.002, 0.379)**	881 (1479.1)	5	0.338 (0.110, 0.789)
Have Six or More Drinks on One Occasion (AUDIT)						
No	1167 (1911.1)	5	0.262 (0.085, 0.611)	1157 (1191.8)	8	0.419 (0.181, 0.825)
Yes	1466 (2398.5))	2	0.083 (0.010, 0.301)	1495 (2452.9)	7	0.285 (0.115, 0.588)
Any History of Rectal Gonorrhea, Rectal Chlamydia, or Syphilis in the Past 24 Weeks						
Yes	709 (1151.9)	3	0.260 (0.054, 0.761)	706 (1150.7)	11	0.956 (0.477, 0.761)
No	1961 (3217.8)	4	0.124 (0.034, 0.318)	1959 (3235.5)	4	0.124 (0.034, 0.317)
Any History of Rectal Gonorrhea in the Past 24 Weeks						

Yes	272 (430.8)	2	**0.464 (0.056, 1.677)**	261 (417.3)	3	0.719 (0.148, 2.101)
No	2398 (3939.0)	5	0.127 (0.041, 0.296)	2404 (3968.8)	12	0.302 (0.156, 0.528)
Any History of Rectal Chlamydia in the Past 24 Weeks						
Yes	342 (562.1)	3	**0.534 (0.110, 1.560)**	333 (536.1)	6	**1.119 (0.411, 2.436)**
No	2328 (3807.6)	4	0.105 (0.029, 0.269)	2335 (3850.0)	9	0.234 (0.107, 0.444)
Any History of Syphilis in the Past 24 Weeks						
Yes	227 (378.9)	0	**0 (*, 0.974)**	261 (430.9)	5	**1.160 (0.377, 2.708)**
No	2442 (3989.7)	7	0.176 (0.071, 0.362)	2404 (3955.2)	10	0.253 (0.121, 0.465)
Use Condoms to Manage HIV Risk at Screening						
Yes	1012 (1658.0)	3	0.181 (0.037, 0.529)	1040 (1710.3)	2	0.117 (0.014, 0.422)
No	1644 (2687.8)	4	0.149 (0.041, 0.381)	1609 (2653.2)	13	0.490 (0.261, 0.838)
Ask Partners Use Condoms to Manage HIV Risk at Screening						
Yes	684 (1120.7)	1	0.089 (0.002, 0.497)	690 (1156.5)	4	0.346 (0.094, 0.886)
No	1972 (3225.1)	6	0.186 (0.068, 0.405)	1959 (3207.1)	11	0.343 (0.171, 0.614)
Ethnicity						
Hispanic	628 (1021.0)	3	0.294 (0.061, 0.859)	673 (1101.7)	3	0.272 (0.056, 0.796)
Non-Hispanic	2041 (3348.6)	4	0.119 (0.033, 0.306)	1990 (3280.9)	12	0.366 (0.189, 0.639)
Circumcised at Screening (CASI)						
Yes	1470 (2429.5)	2	0.082 (0.010, 0.297)	1496 (2505.0)	10	0.392 (0.191, 0.734)
No	1176 (1900.8)	5	0.263 (0.085, 0.614)	1149 (1852.6)	5	0.270 (0.088, 0.630)
RAI Partners in the Last 90 Days Prior to Screening (CASI)						
≤3 RAI Partners	1347 (2208.4)	2	0.091 (0.011, 0.327)	1388 (2297.9)	2	0.087 (0.011, 0.314)
>3 RAI Partners	1231 (2011.3)	5	0.249 (0.081, 0.580)	1181 (1931.9)	13	0.673 (0.358, 1.151)
URAI Partners in the Last 90 Days Prior to Screening (CASI)						
≤3 URAI Partners	1843 (3018.0)	3	0.099 (0.020, 0.290)	1891 (3134.5)	8	0.255 (0.110, 0.503)
>3 URAI Partners	735 (1201.7)	4	0.333 (0.091, 0.852)	678 (1095.3)	7	0.639 (0.257, 1.317)
IAI Partners in the Last 90 Days Prior to Screening (CASI)						
≤3 IAI Partners	1279 (2085.9)	4	0.192 (0.052, 0.491)	1282 (2118.5)	9	0.425 (0.194, 0.806)
>3 IAI Partners	1299 (2133.9)	3	0.141 (0.029, 0.411)	1287 (2111.3)	6	0.284 (0.104, 0.619)
UIAI Partners in the Last 90 Days Prior to Screening (CASI)						
≤3 UIAI Partners	1747 (2848.3)	4	0.140 (0.038, 0.360)	1765 (2902.7)	9	0.310 (0.142, 0.589)
>3 UIAI Partners	831	3	0.219	804	6	0.452

	(1371.4)		(0.045, 0.639)	(1327.1)		(0.166, 0.984)
Baseline Rectal Gonorrhea Local Lab						
Positive	121 (193.4)	0	0 (*, 1.907)	112 (181.9)	2	1.099 (0.133, 0.971)
Negative	2514 (4118.4)	6	0.146 (0.053, 0.317)	2525 (4154.7)	13	0.313 (0.167, 0.535)
Baseline Urine Gonorrhea Covance Lab						
Detected	17 (27.4)	0	0 (*, 13.471)	12 (12.7)	1	6.38 (0.162, 35.58)
Not Detected	2579 (4221.5)	7	0.166 (0.067, 0.342)	2572 (4240.9)	14	0.330 (0.180, 0.342)
Baseline Oral Gonorrhea Local Lab						
Positive	101 (156.6)	0	0 (*, 2.356)	128 (209.4)	3	1.432 (0.295, 4.186)
Negative	2141 (3457.5)	5	0.145 (0.047, 0.337)	2116 (3433.3)	8	0.233 (0.101, 0.459)
Baseline Rectal Chlamydia Local Lab						
Positive	197 (323.1)	0	0 (*, 1.142)	188 (309.6)	4	1.292 (0.352, 3.309)
Negative	2440 (3992.9)	6	0.150 (0.055, 0.327)	2451 (4031.2)	11	0.273 (0.136, 0.488)
Baseline Urine Chlamydia Covance Lab						
Detected	59 (91.4)	2	2.189 (0.265, 7.907)	54 (92.2)	0	0 (*, 4.001)
Not Detected	2537 (4157.5)	5	0.120 (0.039, 0.281)	2530 (4164.4)	15	0.360 (0.202, 0.281)
Baseline Oral Chlamydia Local Lab						
Positive	47 (74.6)	0		42 (66.9)	0	
Negative	2194 (3537.2)	5	0.141 (0.046, 0.330)	2200 (3571.2)	11	0.308 (0.154, 0.551)
Baseline Syphilis Diagnosis						
Yes	7 (10.8)	0		4 (6.5)	0	
No	2663 (4358.9)	7	0.161 (0.065, 0.331)	2661 (4379.7)	15	0.343 (0.192, 0.565)

(some of them may not added up to 2670 and 2665 due to missing information or undetermined category)

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210913Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 208215 SE-012 **SDN:** 419 **DATE REVIEWED:** 08/28/2019
Virology Reviewer: Damon J. Deming, Ph.D.

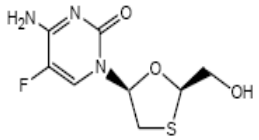
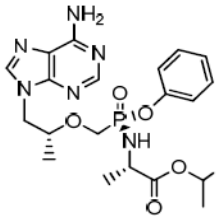
Applicant Name and Address:
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Initial Submission Dates:
Correspondence Date: Apr 05, 2019
Filing Date: May 05, 2019
Review Complete Date: Sep 12, 2019
PDUFA Date: Oct 05, 2019
Electronic Document Room Link:
SE-012 SDN 419 (eCTD 0098)

Additional Submissions Reviewed	Received	Assigned
(b) (4) (b) (4) SDN 006 (eCTD 0005)	Apr 02, 2019	April 02, 2019
NDA 208215 SDN 439 (eCTD 0109)	Jul 03, 2019	July 05, 2019
NDA 208215 SDN 443 (eCTD 0112)	Jul 22, 2019	July 23, 2019
NDA 208215 SDN 445 (eCTD 0113)	Jul 25, 2019	July 26, 2019
NDA 208215 SDN 449 (eCTD 0114)	Aug 02, 2019	Aug 05, 2019
NDA 208215 SDN 452 (eCTD 0117)	Aug 19, 2019	Aug 20, 2019
NDA 208215 SDN 454 (eCTD 0119)	Aug 26, 2019	Aug 27, 2019

Related Supporting Documents: **FTC:** (b) (4), NDA 021500; **TAF:** IND 063737; **FTC/TAF:** IND 111851, IND 127728, NDA 208215

Product Names:
Proprietary: Descovy®
Non-Proprietary/USAN: emtricitabine/tenofovir alafenamide; FTC/TAF; F/TAF

Individual Component	FTC	TAF
Structure		
Chemical Names	5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine	L-Alanine,N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-,1-methylethyl ester,(2E)-2-butenedioate (1:1)
Molecular Formula	$C_8H_{10}FN_3O_3S$	$C_{25}H_{33}O_9N_6P$
Molecular Weight	247.24	592.54
Drug Class	NRTI	NRTI
Supporting Document	(b) (4); IND 053971; NDA 21500	IND 063737; IND 111007; NDA 207561

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 208215 SE-012 **SDN:** 419 **DATE REVIEWED:** 08/28/2019
Virology Reviewer: Damon J. Deming, Ph.D.

Indication: Pre-exposure prophylaxis of sexually acquired HIV-1 infection (PrEP) in men and transgender women who have sex with men
Dosage Form: Tablet (FTC 200 mg/ TAF 25 mg [redacted] (b) (4))
Route of administration: Oral

Abbreviations:

Ab/Ag, HIV-1 antibody/p24 antigen; ANDA, Abbreviated New Drug Application; ART, antiretroviral therapy; ARV, antiretroviral drug; CDC, Centers for Disease Control; CI, confidence interval; DVY, Descovy®; FAS, Full Analysis Set; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type; 1 IU, international unit; LLOQ, lower limit of quantification; LOD, limit of detection; mL, milliliter; MSM, men who have sex with men; NNRTI, non-nucleos(t)ide analog HIV-1 reverse transcriptase inhibitor; NRTI, nucleos(t)ide analog HIV-1 reverse transcriptase inhibitor; PBMC, peripheral blood mononuclear cells; PI, protease inhibitor; PK, pharmacokinetics; PrEP, HIV-1 pre-exposure prophylaxis; PY, person-years; QD, “quaque die” once daily; RT, reverse transcriptase; RT-PCR, reverse transcriptase polymerase chain reaction; sNDA, supplemental New Drug Application; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TFV-DP, tenofovir diphosphate; TGW, transgender women; TMA, transcription-mediated amplification; TVD, Truvada®

Dispensed: Rx _X__ OTC____

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 208215 SE-012 **SDN:** 419 **DATE REVIEWED:** 08/28/2019
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Table of Contents

1 Executive Summary

1.1 Recommendations

This supplemental NDA (sNDA) was submitted to support the expansion of the indication of Descovy® to include the pre-exposure prophylaxis (PrEP) of sexually acquired human immunodeficiency virus type 1 (HIV-1) infection. The sponsor's proposed indication was for the "pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg" and was intended to include both men and women. However, the lack of efficacy data from females is concerning because pharmacokinetics (PK) data from single-dose studies indicate that tenofovir alafenamide (TAF) might be less efficient than tenofovir disoproxil fumarate (TDF) for delivering the active metabolite, tenofovir diphosphate (TFV-DP), to the cells of the female genital tract. Given the uncertainty of the significance of drug levels within the mucosa that are exposed to virus for PrEP efficacy, extrapolating the results of an efficacy trial that was limited to men who have sex with men and transgender women is challenging. However, an approval for a more limited indication for men and transgender women who have sex with men and who are at risk of acquiring sexually transmitted HIV-1 infection (i.e., the populations that were evaluated in a phase 3 trial) is appropriate from a Clinical Virology perspective. An efficacy trail in females at risk of vaginally acquired HIV-1 infection is recommended before extending the indication to that population.

1.2 Summary of Virology Assessments

Nonclinical Virology

The combination of orally administered emtricitabine (F, FTC) and TAF prevented the infection of macaques by chimeric simian/human immunodeficiency virus type 1 (SHIV) following multiple rectal or vaginal exposures. Interestingly, TAF monotherapy provided less protection when used as PrEP in these models.

Clinical Virology

One trial was conducted to support this sNDA, GS-US-412-2055 (DISCOVER; NCT02842086), "*A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are at Risk of HIV-1 Infection*." The results of this trial indicated that Descovy® (F/TAF) was non-inferior to Truvada® (F/TDF) for PrEP. The detection of drug-resistant viruses among participants who became infected during the trial was limited to variants expressing M184I and/or M184V in the viral reverse transcriptase, substitutions that are known to confer resistance to emtricitabine. The resistant viruses were detected in 4 participants who were suspected of being acutely infected at the time they began F/TDF for PrEP. These results are consistent with those of earlier trials that evaluated Truvada® for PrEP.

2 Administrative Signatures

Reviewer's Signature

_____

Damon J. Deming, Ph.D.

Virology Reviewer, Division of Antiviral Products

Concurrence

_____

Julian J. O'Rear, Ph.D.

Virology Team Leader, Division of Antiviral Products

3 Introduction and Background

This supplemental New Drug Application (sNDA) was submitted to support the expansion of the indication for Descovy® (DVY; NDA 208215, approved April 04, 2016), a fixed-dose combination of emtricitabine (F, FTC; Emtriva®, NDA 021500 and multiple Abbreviated New Drug Applications [ANDAs]; initially approved on July 02, 2003) and tenofovir alafenamide (TAF; initially approved as a component of Genvoya® [cobicistat/elvitegravir/F/TAF]; NDA 207561, approved November 05, 2015) for pre-exposure prophylaxis (PrEP) in adults and adolescents at risk of sexually acquired HIV-1 infection. Truvada® (TVD), a fixed-dose combination of FTC and tenofovir disoproxil fumarate (TDF; Viread®; NDA 021356 and multiple ANDAs, initially approved October 26, 2001), was approved for PrEP in adults at risk of sexually acquired HIV-1 infection on July 16, 2012 (NDA 021752 SE-030) and in adolescents at risk of sexually acquired HIV-1 infection on May 15, 2018 (NDA 021752 SE-055).

TAF, like TDF, is a prodrug of the nucleotide analog HIV-1 reverse transcriptase inhibitor (NRTI), tenofovir (TFV). However, TAF is more stable than TDF in plasma and is more efficient at delivering TFV into cells, thereby resulting in higher intracellular concentrations of the active moiety, tenofovir diphosphate (TFV-DP), and lower plasma concentrations of TFV (reviewed by Ray et al., 2016). Differences in the tissue distribution of the hydrolases, kinases, or efflux transporters may also contribute to differences in the distribution of the active TFV-DP moiety following the use of TAF or TDF (Callebaut et al., 2015; Birkus et al., 2016; Cottrell et al., 2017). TAF may also have improved bone and renal safety profiles relative to those of TDF due to reduced off-target effects (Hill et al., 2018).

The combination of F/TAF has been approved, either alone or as part of a combination of antiretroviral drugs (ARVs), as (presented in order of approval):

- Genvoya® (cobicistat/elvitegravir/F/TAF; NDA 207561, approved November 05, 2015)
- Odefsey® (rilpivirine/F/TAF; NDA 208351, approved March 1, 2016)
- Descovy® (F/TAF; NDA 208215, approved April 4, 2016)
- Vemlidy® (TAF for the treatment of hepatitis B virus [HBV] infection; NDA 208464, approved November 10, 2016)
- Biktarvy® (bictegravir/F/TAF; NDA 210251, approved February 07, 2018)
- Symtuza® (cobicistat/darunavir/F/TAF; NDA 210455, approved July 17, 2018)

One trial was conducted to support this sNDA, GS-US-412-2055 (DISCOVER; NCT02842086), "*A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are At Risk of HIV-1 Infection*." Please refer to the Clinical Virology reviews of the original trial protocol submitted in SDN 001 and major amendments in SDNs 004 and 005.

4 Methodology

4.1 HIV-1 Diagnostics

HIV-1 infection status was assessed at Screening, Baseline (Day 1), and Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96, and then every 12 weeks. HIV-1 diagnostic assays were conducted locally using a third-generation HIV-1/HIV-2 antibody test or fourth-generation HIV-1/HIV-2 antibody/p24 antigen (Ab/Ag) test, as available, or at a central laboratory (Covance Inc.) using a fourth-generation HIV-1/HIV-2 Ab/Ag test. If the result of the test conducted at Screening was positive, then the test was repeated, and the

individual was not enrolled into the trial if the retest was positive. If the result of a rapid test conducted during the trial was positive, then the rapid test was repeated. If the rapid retest was positive, then a qualitative or quantitative reverse transcriptase polymerase chain reaction (RT-PCR) or qualitative transcription-mediated amplification (TMA) HIV-1 RNA assay was completed, and a sample collected for possible Sanger-based nucleotide sequence analysis. In addition, an RT-PCR or TMA HIV-1 RNA assay was performed for any participants who showed symptoms consistent with acute infection or who reported a recent exposure considered to be high-risk for HIV-1 infection and a sample for possible genotypic resistance testing collected, regardless of the results of the rapid tests. Surprisingly, samples were not stored for retrospective RT-PCR analysis of HIV-1 RNA to more accurately determine the initial time of infection (as opposed to time of seroconversion) among participants who seroconverted during the trial.

4.2 Plasma HIV-1 RNA Load Determinations

HIV-1 RNA was quantified using the COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0 (Roche Molecular Systems, Inc.) assay, which has a lower limit of quantification (LLOQ) and limit of detection (LOD) of 20 copies/mL.

4.3 Genotypic Resistance Analyses

Plasma samples from the HIV Infection Visit with HIV-1 RNA ≥ 400 copies/mL were analyzed using the GenoSure™ MG assay (Monogram Biosciences), a Sanger sequencing-based assay that is sensitive for variants present at frequencies as low as 10% of the total population (GenoSure™ MG Assay Validation Report Summary).

5 Prior FDA Virology Reviews

Supporting nonclinical and clinical virology studies for FTC, TDF, and TAF were previously reviewed under NDA 021500, NDA 021356, and NDA 207561, respectively. Specifically, the Clinical Virology reviews of NDA 021500 for FTC (reviewed by Narayana Battula, Ph.D.) and NDA 207561 for TAF (reviewed by Lisa Naeger, Ph.D.) contain detailed descriptions of the nonclinical and clinical virology studies used to support approval of FTC and TAF for the treatment of HIV-1 infection, respectively. These data are also summarized in Section 12.4 of the Descovy® label. In addition, supporting nonclinical and clinical virology studies for TVD for PrEP were reviewed under NDA 021752 SE-030 (reviewed by Damon Deming, Ph.D.).

6 Nonclinical Virology

6.1 F/TAF for PrEP in a Non-human Primate SHIV Rectal Challenge Model

The sponsor provided a nonclinical study report (PC-412-2001; also published by Massud et al., 2016) for an experiment in rhesus macaques conducted by the Centers for Disease Control (CDC). Using a design similar to a CDC study that evaluated F/TDF for PrEP in rhesus macaques (García-Lerma et al., 2010), the investigators determined that oral administration of F/TAF can prevent infection with a chimeric simian/human immunodeficiency type 1 virus (SHIV) following intrarectal challenge.

The investigators selected a 1.5 mg/kg dose of TAF for the macaque study based on the results of a preliminary pharmacokinetics (PK) study. Specifically, the intracellular concentrations of TFV-DP in

peripheral blood mononuclear cells (PBMC) following the 1.5 mg/kg dose in macaques were consistent with those observed in humans receiving a single 25 mg dose of TAF. The oral administration of 20 mg/kg FTC in macaques was also consistent with human PK profiles following the administration of a single 300 mg dose (García-Lerma et al., 2010). It is unclear how well the drug PK profiles in blood, rectal, and genital tissues of macaques compare to those of humans after achieving steady state concentrations.

Twelve rhesus macaques were intrarectally challenged once-weekly with 1 mL of inoculum containing 10 $TCID_{50}$ ($7.6x10^5$ RNA copies) of the CCR5-tropic $SHIV_{SF162p3}$, a chimeric virus that contains the *tat*, *rev*, and *env* coding regions of $HIV\text{-}1_{SF162}$ in a SIV_{mac239} background. Of note, the chimeric virus reverse transcriptase (RT), the target of FTC and TAF, is derived from SIV, not HIV-1. Each weekly challenge took place 24 hours after receiving F/TAF or placebo (saline solution) by oral gavage, and a second dose of F/TAF or placebo was administered 2 hours after each challenge. The SHIV challenges and paired gavages were administered once a week for up to 19 weeks, as illustrated in Figure 1 (pg. 8, PC-412-2001). None (0/6) of the animals receiving F/TAF became infected while all (6/6) of the macaques given placebo became infected with SHIV (Figure 2; pg. 8, PC-412-2001). These results are similar to those of macaques receiving F/TDF in García-Lerma et al., 2010, where 5/6 animals were protected from infection after 14 challenges and 9/9 placebo animals became infected. No evaluation of resistance appears to have been conducted as part of this experiment.

García-Lerma et al., 2011 evaluated the prophylactic activity of TAF monotherapy when dosed at 13.7 mg/kg three days before intrarectal challenge using their macaque model. Interestingly, 4/6 of the animals receiving this high dose of TAF were infected by the 5th challenge, after which time the challenge series was halted due to inadequate activity. The investigators hypothesized that the lack of prophylactic activity, which was observed despite higher tissue levels of TFV and TFV-DP than those achieved by TDF, was due to high levels of intracellular dATP, which TFV-DP competes with for incorporation into nascent HIV-1 transcripts, in rectal lymphocytes. The sponsor also pointed out that the dosing regimen lacked FTC and was different than that used in the García-Lerma et al., 2010 F/TDF experiment (i.e., 3 days prior to challenge vs. 22 hours before and 2 hours after challenge). In addition, Subarrao et al., 2006 reported that TDF monotherapy dosed orally once-daily or once-weekly at 20 mg/kg also failed to protect macaques from rectal SHIV challenge, potentially indicating that TFV-based monotherapy might be incapable of preventing infection in this model. The researchers reported that no TFV-resistant virus, defined as HIV-1 reverse transcriptase (RT) K65R-expressing variants, were detected among the 4 PrEP failures despite continuing to have received once-weekly doses of TAF for 12 to 14 weeks after becoming infected. It is unclear whether TFV resistance-associated substitutions at RT K70 were assessed. The assay used to assess resistance was not identified.

Figure 1: Design of once-weekly challenge experiment

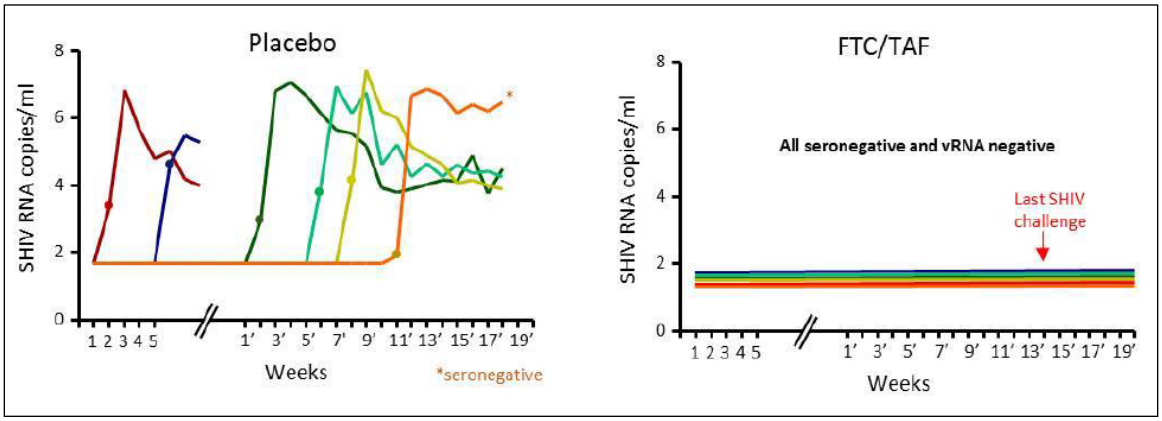

Figure 2: SHIV RNA from Study PC-412-2001

6.2 F/TAF for PrEP in a Non-human Primate SHIV Vaginal Challenge Model

A follow-up study from the CDC evaluated the ability of F/TAF to prevent SHIV infection of pigtail macaques following vaginal challenges (Massud et al., 2019). The investigators confirmed in a preliminary experiment that orally administered 20 mg/kg FTC and 1.5 mg/kg TAF used in the rhesus macaque rectal SHIV challenge studies yielded similar PK profiles in pigtail macaques.

The design of this study was similar to the previous macaque studies that evaluated F/TAF. Twelve healthy pigtail macaques were vaginally challenged once-weekly with 1 mL of inoculum containing 50 $TCID_{50}$ of $SHIV_{SF162p3}$. Each weekly challenge took place 24 hours after receiving F/TAF or placebo (saline solution) by oral gavage, and a second dose of F/TAF or placebo was administered 2 hours after each challenge. The SHIV challenges and paired gavages were administered once a week for up to 15 weeks. One (1/6) of the animals receiving F/TAF became infected while all (6/6) of the macaques given placebo became infected with SHIV. These results are similar to those of macaques receiving F/TDF in Radzio et al., 2012, where 0/6 animals became infected after up to 18 challenges and 6/6 placebo animals became infected. Interestingly, the animal that received F/TAF but became infected had unexpectedly low levels of TFV-DP in PBMCs at most timepoints, potentially indicating problematic drug administrations in the animal.

Massud et al., 2019 also evaluated the prophylactic activity of TAF monotherapy when dosed at 1.5 mg/kg 24 hours before and 2 hours after vaginal challenge. Interestingly, only 4/9 of the animals that received TAF remained uninfected. Although 2/5 of these animals demonstrated low TFV-DP concentrations in PBMCs, the 3 remaining animals that became infected demonstrated TFV-DP concentrations comparable to those of the animals that remained uninfected. These results are consistent with those of the rectal challenge study that indicated limited protection by TAF monotherapy.

No FTC-resistant variants, defined as those expressing RT M184I or M184V, or TFV-resistant variants, defined as those expressing RT K65R or K70E, were detected in animals that became infected by allele-specific RT-PCR or by next-generation sequencing (NGS) analyses.

7 Clinical Virology

7.1 GS-US-412-2055 (NCT02842086)

Study GS-US-412-2055 is an ongoing randomized, double-blinded trial to compare the safety and efficacy of DVY versus TVD administered orally once daily for at least 96 weeks in HIV-1 negative adult men who have sex with men (MSM) and transgender women (TGW) who are at risk of acquiring HIV-1 infection through sexual exposure to men. Eligible participants who provided written consent were randomized in a 1:1 ratio to 1 of the following 2 treatment groups:

Group 1: DVY (200/25 mg) + placebo-to-match TVD
Group 2: TVD (200/300 mg) + placebo-to-match DVY

A total of 5,387 participants (DVY=2,694 participants; TVD=2,693 participants) were enrolled from 94 trial sites in the United States (n=3,220), Austria (n=77), Canada (n=353), Denmark (n=202), France (n=32), Germany (n=370), Ireland (n=78), Italy (n=58), Netherlands (n=71), Spain (n=414), and the United Kingdom (n=512). All participants were biologically male at birth, with 98.6% (n=5,313) identified as MSM and 1.4% (n=74) identified as TGW. Participants were randomized and received at least 1 dose of study drug. The Full Analysis Set population, which was used to evaluate primary safety and efficacy endpoints, consisted of 5,335 participants (DVY = 2,670 participants; TVD = 2,665 participants) with a minimum follow-up of 48 weeks and at least 50% with 96 weeks of follow-up.

Twenty-two infections occurred among study participants by the time of the sNDA submission, with 7 of the infections occurring among participants randomized to the F/TAF group and 15 infections occurring among participants randomized to the F/TDF group. An additional infection in a participant ([redacted] (b) (6)) in the F/TAF group was reported in the 90-Day Safety Update (SDN 439), yielding a total of 23 infections, with 8 occurring among participants in the F/TAF group and 15 in the F/TDF group. The prophylaxis failures are listed in Table 1 (Reviewer's summary) along with the country in which they were enrolled, the Study Day (and Week) of the last negative and first positive serology based HIV-1 diagnostic assays, and the HIV-1 seroconversion window (time between first positive and last negative tests).

The sponsor determined that 1 participant in the F/TAF group ([redacted] (b) (6) and 4 participants in the F/TDF group ([redacted] (b) (6)) were likely acutely infected at study entry, although other participants in both the F/TAF group ([redacted] (b) (6) and [redacted] (b) (6) and F/TDF group ([redacted] (b) (6)) might also have been infected at baseline given their short times to seroconversion (i.e., within the first 2 months of the study). Surprisingly, the sponsor did not retrospectively conduct an assay specific for HIV-1 RNA using stored samples collected at baseline and screening to provide additional insight into the infection status of these individuals at the time PrEP was initiated.

The primary efficacy endpoint was the incidence of HIV-1 infection per 100 person-years (PY), which was calculated as the number of participants who became infected divided by the sum of the participants' years of follow-up during the study. The primary endpoint was assessed when all participants had a minimum follow-up of 48 weeks and at least 50% of participants had completed their Week 96 visit or had permanently discontinued from the study. The HIV-1 infection rate was 0.160 per 100 PY (95% confidence interval [CI]: 0.064 to 0.330 per 100 PY) for F/TAF and 0.342 per 100 PY (95% CI: 0.191 to 0.564 per 100 PY) for F/TDF, indicating that there was no statistically significant difference between the study groups and that F/TAF was noninferior to F/TDF. These results were not

affected by inclusion of the 23rd infection or exclusion of the 5 participants who were believed to have been acutely infected at baseline; indeed, these changes reduce the difference between the incidence rates of the study groups.

Table 1: HIV-1 diagnostics for participants who became infected during the trial

ARM	Subject	Country	Last Negative Result Day (Week)	First Positive Result Day (Week)	Seroconversion Window Days (Weeks)
F/TAF	(b) (6)	USA	337 (48)	408 (58)	71 (10)
F/TAF		USA	598 (85)	679 (97)	81 (12)
F/TAF		USA	505 (72)	589 (84)	84 (12)
F/TAF		CAN	1 (0)	29 (4)	28 (4)
F/TAF		DEU	186 (27)	234 (33)	48 (7)
F/TAF		ESP	499 (71)	589 (84)	90 (13)
F/TAF		ESP	31 (4)	95 (14)	64 (9)
F/TAF		ESP	30 (4)	82 (12)	52 (7)
F/TDF		USA	342 (49)	420 (60)	78 (11)
F/TDF		USA	338 (48)	372 (53)	34 (5)
F/TDF		USA	1 (0)	29 (4)	28 (4)
F/TDF		USA	420 (60)	506 (72)	86 (12)
F/TDF		USA	29 (4)	85 (12)	56 (8)
F/TDF		USA	149 (21)	219 (31)	70 (10)
F/TDF		USA	335 (48)	420 (60)	85 (12)
F/TDF		USA	1 (0)	29 (4)	28 (4)
F/TDF		USA	672 (96)	755 (108)	83 (12)
F/TDF		USA	583 (83)	615 (88)	32 (5)
F/TDF		CAN	88 (13)	184 (26)	96 (14)
F/TDF		CAN	37 (5)	126 (18)	89 (13)
F/TDF		USA	425 (61)	474 (68)	49 (7)
F/TDF		GBR	144 (21)	228 (33)	84 (12)
F/TDF		USA	1 (0)	36 (5)	35 (5)

Nineteen of the individuals who seroconverted during the trial had samples collected near the time of seroconversion that were suitable for genotypic resistance analysis (e.g., HIV-1 RNA >400 copies/mL), including 6 participants from the F/TAF group and 13 participants from the F/TDF group (Table 2; Reviewer's summary). Eighty-four percent (16/19) of the participants who seroconverted during the trial were infected with subtype B viruses, 11% (2/19) with subtype F1, and 5% (1/19) with subtype AG. Viruses expressing substitutions that confer resistance to NRTIs, including D67N, M184I/V, and K219E, were detected in 5 participants. Viruses expressing substitutions known to confer resistance to FTC specifically, including M184I and/or M184V, were detected in 4 participants, all of whom received F/TDF and were suspected to have been infected before beginning PrEP.

Interestingly, the presence of viruses expressing non-nucleos(t)ide analog HIV-1 reverse transcriptase inhibitor (NNRTI) resistance-associated substitutions, including K103N, Y188L, T215I/E/S (possible revertants from T215F/Y), and L324I indicate that these study participants may have been infected with viruses from treatment-experienced sexual partners. Although it is possible that M184I/V-expressing variants may also have been acquired rather than selected by F/TDF used for PrEP, these variants have been reported to be only infrequently (<0.2%) transmitted (Margot et al., 2017), although the

analyses conducted by Margot et al., 2017 relied upon Sanger nucleotide sequencing-based assays, which might have lacked the sensitivity to detect minority variants expressing M184V. Indeed, Wainberg et al., 2011 reported that M184V-expressing variants were frequently detected (~23%) in one cohort of acutely infected individuals when using a sensitive allele-specific RT-PCR assay, a detection rate that was ~3-fold higher than that achieved by a Sanger-based assay. Another potential limitation of the Margot et al., 2017 study is that the time of sampling relative to the time of infection is unclear. Margot et al., 2017 reported the frequency of treatment-naïve trial participants harboring viruses with ARV resistance-associated substitutions. However, these participants were not necessarily acutely infected, and it is possible that any M184V-expressing variants were overgrown by more replication competent wild-type virus by the time of evaluation. Variants expressing M184V may diminish to undetected levels within weeks in acutely infected individuals (Wainberg et al., 2011). In any case, the sponsor did not collect HIV-1 RNA at baseline, which might have allowed for genotypic analyses of virus before the acutely infected participants started PrEP and allowed for a more definitive determination of whether the M184V-expressing variants were transmitted or selected from acquired wild-type virus.

Table 2: HIV-1 RT resistance-associated substitutions from virus collected at seroconversion

						HIV-1 Reverse Transcriptase							
Arm	Subject	Country	Day	Subtype	HIV-1 RNA (copies/mL)	D067	K103	V106	M184	Y188	T215	K219	L234
F/TAF	(b) (6)	USA	421	B	199000								
F/TAF		USA	589	B	2900								
F/TAF		DEU	234	B	592000								
F/TAF		ESP	589	B	242000								
F/TAF		ESP	95	F1	141000								
F/TAF		ESP	82	B	2780			I					
F/TDF		USA	420	B	5340								
F/TDF		USA	372	B	8610								
F/TDF		USA	38	B					M/I/V		T/I		
F/TDF		USA	511	B	1280000								
F/TDF		USA	29	B	1150				V				
F/TDF		USA	85	B	407				V				
F/TDF		USA	425	B	211000						E		
F/TDF		USA	34	B	576		N		M/I/V		T/S		
F/TDF		USA	667	F1	567	D/N							
F/TDF		USA	674	F1	792								
F/TDF		CAN	191	B	5040		N						
F/TDF		CAN	126	AG	8070000								
F/TDF		USA	489	B	1070000			I					
F/TDF		GBR	229	B	79145								
F/TDF		USA	36	B	18700	G			V	L		E	I

Genotypic data for Subject (b) (6), who was identified as infected in the 90-Day Safety Update (SDN 439), were not provided, although the narrative describing this participant's case stated that "Monogram genotype demonstrates sensitivity to all drugs tested," presumably indicating that no M184I/V-expressing variants were detected. In addition, there was discordant resistance information provided for Participant (b) (6). An investigator stated in a narrative that an M184V-expressing variant was detected; however, no such variant was reported in the resistance dataset included in the sNDA submission. The sponsor was asked about this apparent discrepancy and responded (SDN 445) that no M184V-expressing variants were detected by Monogram, the trial's central laboratory, using the validated GenoSure™ MG assay. The sponsor stated that the sample provided to Monogram was drawn one day before the sample used for the local genotypic assay, so it is unlikely that a significant shift in the viral quasi-species occurred in that time. The sponsor also noted that they have no information about the relative accuracy of the local assay used by the investigator and stated that they are currently performing additional genotypic analyses for all participants who became infected in the DISCOVER trial using ultra-sensitive nucleotide sequencing assays in a central lab at the University of Pittsburgh. The results will be provided to the Agency for review when available.

Study drug adherence was evaluated in participants who became infected by quantifying TFV-DP concentrations in dried blood spots (DBS) and estimating the number of doses of F/TAF or F/TDF taken per week to achieve those concentrations (Anderson et al., 2018). The TFV-DP concentration categories used to evaluate adherence for F/TAF were <450 fmol/punch (low: <2 doses/week), 450 to <900 fmol/punch (medium: 2 to 3 doses/week), and ≥900 fmol/punch (high: ≥4 doses/week. The categories used to evaluate adherence for F/TDF were <350 fmol/punch (low: <2 doses/week), 350 to <700 fmol/punch (medium: 2 to 3 doses/week), and ≥700 fmol/punch (high: ≥4 doses/week). The TFV-DP data, HIV-1 RNA, time of the last negative HIV-1 diagnostic test, time of the first positive HIV-1 diagnostic test, time of HIV-1 RT M184I/V detection, and adherence estimates are illustrated for participants who seroconverted during the trial and were assigned to use F/TAF in Figure 3 and those assigned to use F/TDF in Figure 4 (Reviewer summary). According to the sponsor, TFV-DP concentrations of ≥700 fmol/punch were associated with effective PrEP by F/TDF. Note that HIV-1 RNA shown at 0 $\log_{10}$ copies/mL and TFV-DP shown at 0 fmol/punch indicate that no analyte was detected.

These data indicate that most participants were non-adherent near or at the time of seroconversion and (presumably) at the time of infection. The most notable exceptions are those participants ((b) (6), (b) (6), and (b) (6)) who were suspected to have been acutely infected at or near baseline when they began to use their assigned study drug. These are also the only subjects harboring HIV-1 RT M184I/V-expressing variants, which is consistent with the supposition that these variants were selected by FTC during PrEP use rather than acquired from an ARV-experienced sexual partner.

There were three participants with missing TFV-DP PK data at the time of seroconversion who otherwise appeared to be at least moderately adherent at earlier timepoints (i.e., (b) (6) (b) (6), and (b) (6)). According to the investigator narratives, Participant (b) (6) reported that he had been off study drug for the 2 weeks prior to the sexual encounter that likely resulted in infection, Subject (b) (6) reported discontinuing PrEP at Week 5, and Subject (b) (6) reported high adherence through the time of seroconversion. The lack of RT M184I/V-expressing variants detected in these participants might indicate that adherence was low between the time of infection and the time to seroconversion detection. Still, it would have been useful to have the TFV-DP PK data from DBS collected at the seroconversion or confirmation visit to verify that there were no PrEP failures that occurred despite high adherence.

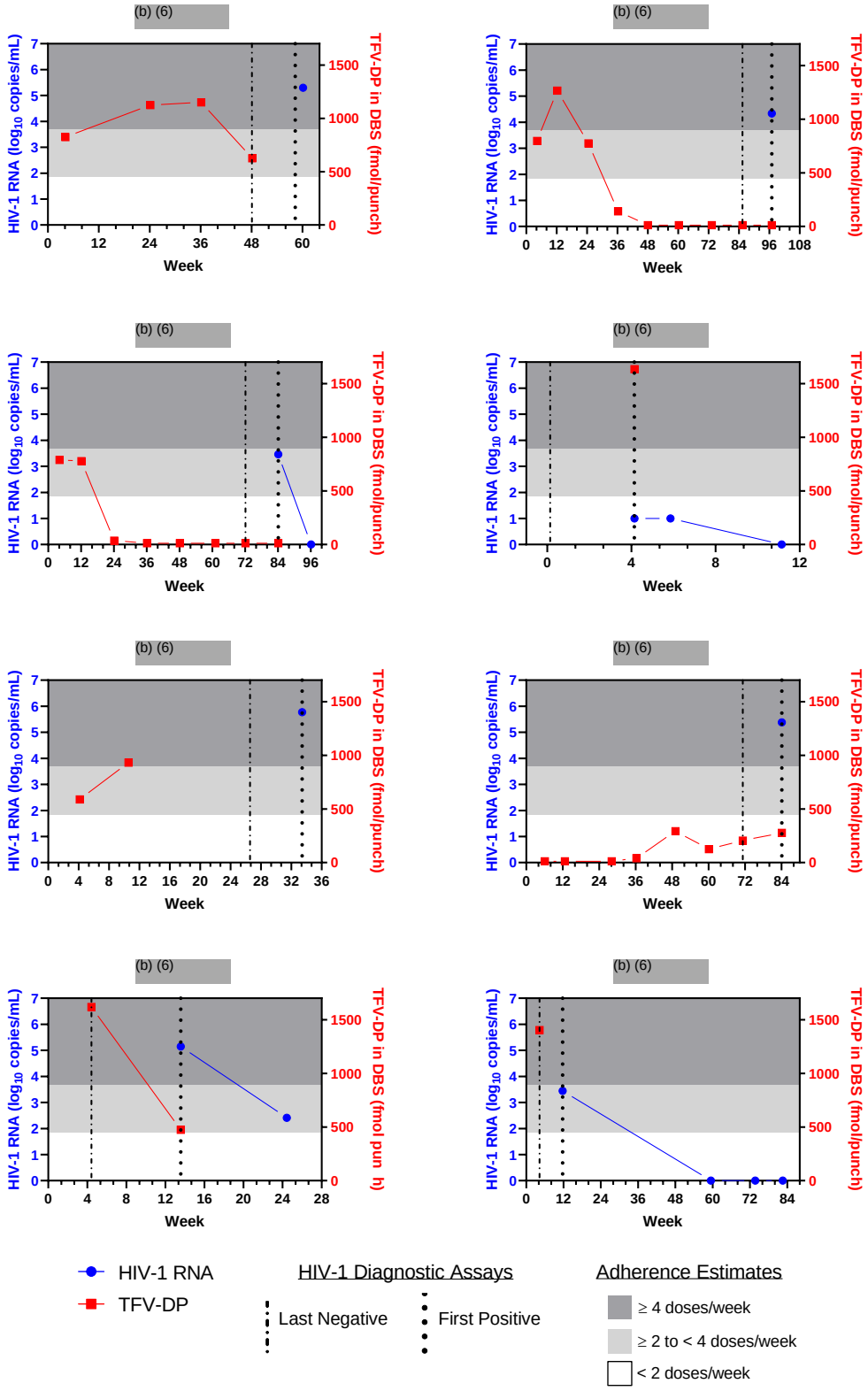

Figure 3: HIV-1 RNA, TFV-DP PK, and seroconversion window in F/TAF PrEP failures

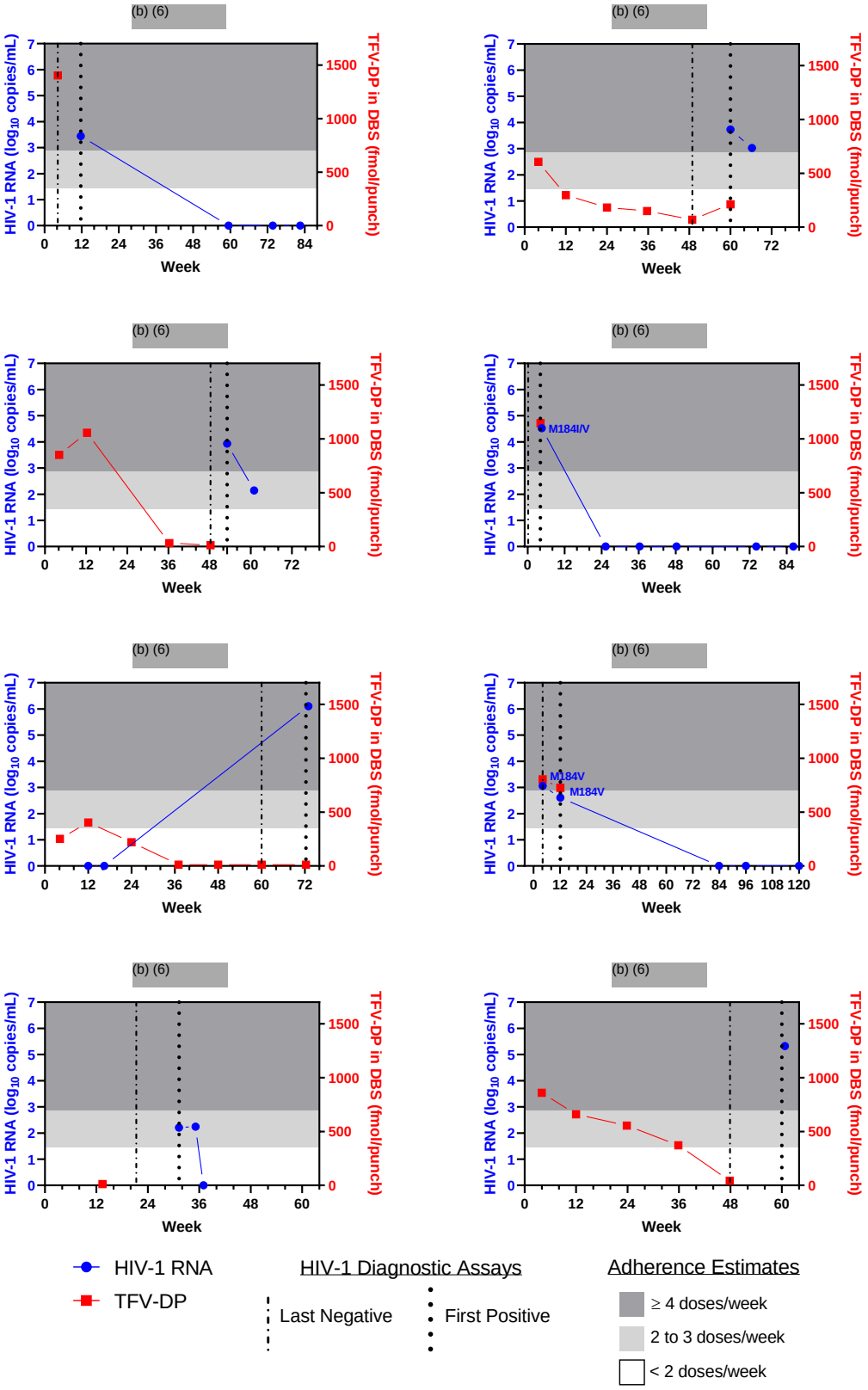

Figure 4: HIV-1 RNA, TFV-DP PK, and seroconversion window in F/TDF PrEP failures

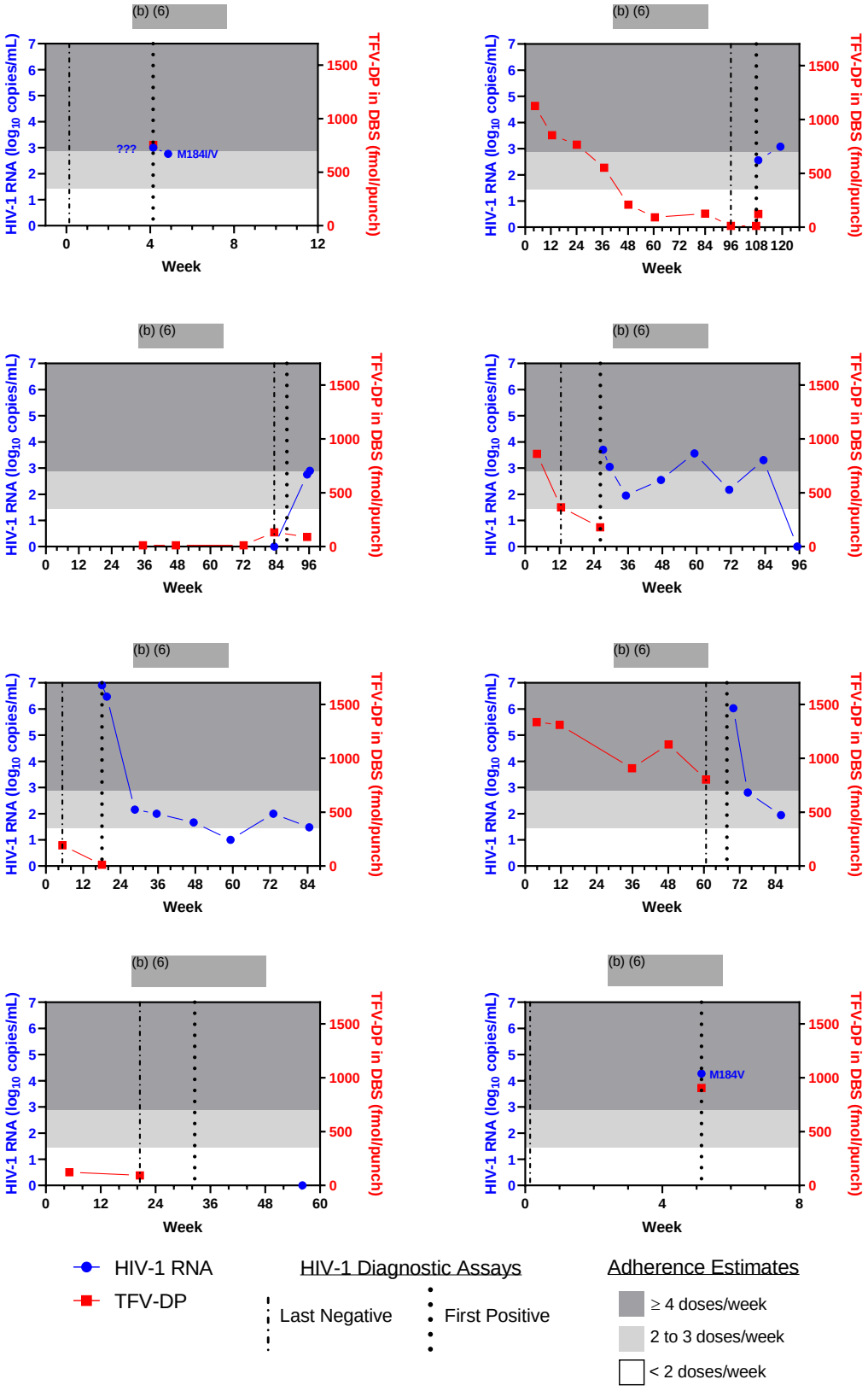

Figure 4: HIV-1 RNA, TFV-DP PK, and seroconversion window in F/TDF PrEP failures (cont'd.)

8 Package Insert

This section summarizes the changes to Section 12.4 of the Descovy® label that were proposed by the sponsor and the proposed edits and additions of the FDA reviewers. The label's current text is presented in black text, the sponsor's proposed changes in red text, and the DAVP reviewers' edits in blue text.

(b) (4)

[redacted]

In Clinical Trials

(b) (4)

[redacted]

The resistance profile of DESCOVY in combination with other antiretroviral agents for the treatment of HIV-1 infection is based on studies of FTC+TAF with EVG+COBI in the treatment of HIV-1 infection. In a pooled analysis of antiretroviral-naïve subjects, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. Genotypic resistance developed in 7 of 14 evaluable subjects. The resistance-associated substitutions that emerged were M184V/I (N=7) and K65R (N=1). Three subjects had virus with emergent R, H, or E at the polymorphic Q207 residue in reverse transcriptase.

One subject was identified with emergent resistance to FTC (M184M/I) out of 4 virologic failure subjects in a clinical study of virologically-suppressed subjects who switched from a regimen containing FTC+TDF to FTC+TAF with EVG+COBI (N=799).

(b) (4)

[redacted]

(b) (4)

9 Conclusions

This supplemental NDA is approvable from a Clinical Virology perspective for the pre-exposure prophylaxis (PrEP) of HIV-1–uninfected male adults and adolescents who are at high risk of sexually acquired HIV-1 infection from men. The sponsor's proposed indication was initially for the "pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg" and was intended to include both men and women. However, the lack of efficacy data from females is potentially concerning because PK data from single-dose studies indicate that TAF might be less efficient than TDF for delivering TFV-DP to the cells of the female genital tract (Patterson et al., 2011; Cottrell et al., 2016; Garrett, CROI 2016; Cotrell et al., 2017), and extrapolating F/TAF PrEP efficacy from MSM and TGW to cisgender women at risk of vaginally acquired HIV-1 infection might therefore be difficult.

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DAMON J DEMING
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210913Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA (Supplement #)	208215 (S-12)
Type of Submission and Proposal	Efficacy supplement to expand indication to pre-exposure prophylaxis of HIV-1 infection (PrEP) in adults and adolescents with body weight at least 35 kg
Submission Date	04/05/2019
Drug	DESCOVY [emtricitabine (FTC, F)/tenofovir alafenamide (TAF)]
Applicant	Gilead
Dosage regimen	One tablet (a fixed dose combination of FTC 200 mg/TAF 25 mg) once daily without regard to food
Clinical Pharmacology Reviewer	Jenny Zheng, Ph.D
Clinical Pharmacology Team Leader	Su-Young Choi, Pharm.D, Ph.D

EXECUTIVE SUMMARY

Descovy (F/TAF) is a fixed-dose combination tablet containing emtricitabine (FTC, F) 200 mg and tenofovir alafenamide (TAF) 25 mg. Descovy is an oral once-daily medication that was approved for use in chronic HIV treatment in combination with other antiretroviral agents. In this supplement, the Applicant seeks approval of Descovy for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg. Currently, Truvada, a fixed-dose combination of FTC 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg, is the only medication approved for PrEP.

To support the proposed indication, the applicant submitted the efficacy and safety results from a Phase 3 clinical trial, Study GS-US-412-2055 (DISCOVER), entitled "*A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men (MSM) and Transgender Women (TGW) Who Have Sex with Men and Are At Risk of HIV-1 Infection*" (NCT02842086). DISCOVER is a noninferiority trial evaluating the incidence of HIV-1 infection per 100 patient years (PY) in subjects who were administered Descovy as compared to that in subjects who were administered Truvada. The multidiscipline review team has determined that the efficacy and safety data from the DISCOVER trial demonstrated that Descovy is non-inferior to Truvada in efficacy and safety for PrEP in MSM and TGW.

No clinical trials were conducted for the PrEP indication in cisgender women or adolescents. The applicant proposed a pharmacokinetic (PK) extrapolation approach to bridge the efficacy data from the DISCOVER trial as well as efficacy data from Truvada to cisgender women or adolescents based on systemic and/or mucosal PK data. To this end, the Applicant provided data from an external PK study, entitled "*Exploratory Pharmacokinetic and Pharmacodynamic Study of Oral F/TAF for the Prevention of HIV Acquisition*" (cross-referenced to (b) (4) , CONRAD Protocol A15-137) and summary of available PK data of Truvada and Descovy in men and women.

An Advisory Committee Meeting was held on August 7, 2019. Sixteen (16) of 18 committee members voted for the approval of a PrEP indication in MSM and TGW, although some members expressed reservations for the approval for TGW due to the limited number of TGW subjects that were included in

the DISCOVER trial. In addition, 10 of 18 committee members were against expanding the PrEP indication to cisgender women due to the lack of efficacy data in this population. The majority of the committee members who voted "Yes" indicated that their reasoning was that another PrEP agent should be available to cisgender women. They also recommended conducting efficacy trials in cisgender women following approval. Based on the review of the submitted data and the advisory committee's recommendation, the clinical pharmacology review team has determined that the available data are inadequate to support the PrEP indication for Descovy in cisgender women.

The clinical pharmacology review team has also concluded that extrapolation of efficacy and safety results from the DISCOVER trial in MSM/TGW adults to male adolescents is acceptable.

RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the application and determined that the efficacy supplement is approvable for adults and adolescent MSM/TGW. However, OCP has concluded that the available PK data are not adequate to support expansion of the PrEP indication to cisgender women.

PHASE 4 TRIAL COMMITMENTS

There are no clinical pharmacology related Phase 4 trial commitments.

LABELING

We recommend the following general labeling recommendations to be included in the final USPI (Clinical Pharmacology relevant sections only). In addition, several changes have been recommended to the applicant to be consistent with current labeling practices and for PLLR conversion.

<u>Section 1 Indication and Usage</u>

- Add PrEP indication. In this section, the Agency
  - recommends adding the limitation to exclude the PrEP indication for receptive vaginal sex and indicate that the safety and efficacy have not been evaluated in individuals at risk of HIV-1 infection from receptive vaginal sex (e.g., cisgender women)
  - agrees with the applicant to add the indication for adolescents weighing at least 35 kg, similar to the Truvada label

<u>Section 2 Dosage and Administration</u>

- Add the dosage for PrEP, which is the same as the treatment indication for Descovy

<u>Section 8 Specific Population - Pediatrics</u>

- Add the information indicating the efficacy and safety for pediatric patients at least 35 kg is supported by the adult PrEP trial and previous safety and PK data from adults and pediatrics
- Add the recommendation and rationale for more frequent visits for at risk adolescents under pediatrics
- Add "Safety and effectiveness of DESCOVY for HIV-1 PrEP in pediatric patients less than 35 kg have not been established" under pediatrics

Section 12.3 Pharmacokinetics

- Add "HIV status has no effect on the pharmacokinetics of FTC or TAF in adults"
- Replace "no dosage adjustment is recommended" with "there are no clinically meaningful differences" for race or gender

QUESTION-BASED REVIEW

Background

The Applicant is seeking an HIV PrEP indication for Descovy for use in at-risk adults and adolescents weighing at least 35 kg. To support the indication, the Applicant conducted a Phase 3 clinical trial in MSM/TGW, Study GS-US-412-2055 (DISCOVER), entitled "*A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are At Risk of HIV-1 Infection"* (NCT02842086). The HIV infection rate per 100 person-years was 0.160 for Descovy and 0.342 for Truvada, and the multidiscipline review team has concluded that the trial demonstrated non-inferiority of Descovy to Truvada in MSM/TGW. However, the Applicant did not conduct an efficacy trial in cisgender women or adolescents. Therefore, the key clinical pharmacology review question is whether the available clinical pharmacology information can support the expansion of the indication to cisgender women and adolescents.

Substantial clinical pharmacology related information used to support the applicant's claim, effectiveness in cisgender women, is from the clinical pharmacology information of Truvada, the only approved product for HIV PrEP. TRUVADA is a fixed-dose combination tablet containing emtricitabine (FTC) 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg. Both TAF (in Descovy) and TDF (in Truvada) are prodrugs and form the active metabolite TFV-DP intracellularly. While the intracellular active metabolite TFV-DP is the same for both drugs, TAF and TDF exhibit distinct PK properties; the administration of TAF 25 mg results in 4- to 7-fold higher intracellular levels of TFV-DP in peripheral blood mononuclear cells (PBMCs) and approximately 90% lower plasma concentrations of TFV compared with TDF 300 mg. Both Truvada and Descovy contain 200 mg of FTC and plasma concentrations of FTC are comparable following administration of each drug. This review will focus on comparison of TAF and TDF component of Descovy and Truvada, respectively, and its implication for extrapolating efficacy of Descovy for HIV PrEP to cisgender women. It should be noted that the exact contribution of FTC to PrEP efficacy, and whether this contribution differs depending on the route of HIV exposure (e.g., rectal vs. vaginal), is largely unknown.

Review Question 1. Can HIV PrEP indication be expanded to cisgender women?

The Applicant proposed two approaches to extrapolate efficacy to support a PrEP indication for F/TAF in cisgender women as follows.

1. To extrapolate efficacy from MSM/TGW receiving F/TAF in the DISCOVER trial by demonstrating comparable plasma TAF concentrations and PBMC TFV-DP concentrations between MSM/TGW and cisgender women.

In this approach, the applicant argues that the efficacy in MSM/TGW observed in the DISCOVER trial can be extrapolated to cisgender women as plasma TAF and TFV-DP in PBMC are comparable between MSM/TGW and cisgender women. However, the unique aspect of sexually acquired HIV infection and pharmacological prevention is that the route of infection is different between cisgender women (mostly receptive vaginal intercourse) and MSM/TGW (mostly receptive or insertive anal intercourse). Currently, the relevant site of drug action to prevent HIV-1 infection, or the relative contribution of tissue versus PBMC drug concentrations to PrEP efficacy, have not been established. However, previous clinical studies using Truvada have indicated that 1) mucosal (rectal vs. vaginal) concentrations of TFV-DP can be significantly different despite similar systemic concentrations and 2) the importance of mucosal tissue concentrations cannot be ignored at this time as topical microbicides demonstrated some level of efficacy despite significantly low TFV-DP concentrations in PBMC. Therefore, although there is no clinically relevant difference in the PK of TAF in plasma and TFV-DP in PBMC between men and women, the clinical pharmacology review team concluded that this approach alone is not acceptable to support the indication in cisgender women due to the potential importance of mucosal tissue concentrations for HIV PrEP efficacy.

2. To extrapolate efficacy from Truvada to Descovy

Truvada is currently approved in adults and adolescents of both sexes, including cisgender women. The efficacy of Truvada in cisgender women was supported by the Partners PrEP trial (NCT00557245) in heterosexual HIV discordant couples. In this approach, efficacy would be extrapolated by demonstrating comparable or higher TFV-DP concentrations in PBMCs and cervicovaginal mucosal tissues following the administration of Descovy as compared with Truvada. Since it has already been demonstrated that TFV-DP concentrations in PBMCs are 4-7-fold higher following the administration of Descovy compared with Truvada, the extrapolation would need to demonstrate comparable or higher exposures of TFV-DP in cervicovaginal tissues following the administration of Descovy compared to Truvada. This is under the assumption that drug concentrations in tissue homogenates are reflective of those in target cells such as local CD4+ cells. To this end, the Applicant provided data from an external PK study, entitled "*Exploratory Pharmacokinetic and Pharmacodynamic Study of Oral F/TAF for the Prevention of HIV Acquisition"* (cross-referenced to (b) (4) , CONRAD Protocol A15-137). In this study, the pharmacokinetics of TAF, TFV, FTC and their intracellular metabolites (TFV-DP and FTC-TP) in PBMCs and PrEP-relevant mucosal tissues and fluids were determined following administration of single and multiple doses (once daily for 14 days) of Descovy or Truvada in HIV-negative, healthy adult female volunteers.

Following single-dose administration of F/TAF or F/TDF, 83% of TFV-DP concentrations in vaginal tissue samples were below the limit of quantitation (BLQ) at 4 hours post-dose. Therefore, it is not feasible to compare TFV-DP concentrations in vaginal tissue samples following single dose administration.

TFV-DP concentrations were higher in vaginal tissues at 4 hours post-dose following 14 days of F/TAF administration as compared with F/TDF; following the administration of F/TAF, median TFV-DP concentrations in vaginal tissues were 3-fold above the lower limit of quantitation (LLOQ) at 4 hours after the last dose. In contrast, 62% (5/8) of vaginal tissue samples were BLQ at this same time point following 14-day administration of F/TDF (Table). It is not feasible therefore to determine the magnitude of difference in vaginal tissue TFV-DP concentrations between the treatment groups due to the limited number of quantifiable samples in the F/TDF arm. In both treatment groups, TFV-DP concentrations were mostly (70-80%) BLQ at 24 hours and 48 hours post-dose following 14 days of administration of F/TAF or F/TDF. Results for cervical tissue samples were largely consistent with those for vaginal tissues.

Table 1: Mucosal Tissue TFV-DP Concentrations Following 14-Day Administration of F/TAF 200/25 mg or F/TDF 200/300 mg (CONRAD Protocol A15-137)

		Vaginal tissue		Cervical tissue		Rectal tissue	
		F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF
4 hours	% BLQ*	0% (0/8)	62% (5/8)	25% (2/8)	88% (7/8)	31% (9/29)	3% (1/30)
	Median TFV-DP† (pmol/g)	151	N/A	126	N/A	150	2521
24 hours	% BLQ*	80% (12/15)	69% (11/16)	10/15 (67%)	81% (13/16)	Not Collected	
	Median TFV-DP† (pmol/g)	N/A	N/A	N/A	N/A		
48 hours	% BLQ*	80% (12/15)	79% (11/14)	93% (14/15)	100% (14/14)		
	Median TFV-DP† (pmol/g)	N/A	N/A	N/A	N/A		

* Percentage of samples below the lower limit of quantitation (BLQ) = number of samples BLQ/ total number of samples
† Median values of all subjects including those with a value of BLQ
N/A = cannot be determined as the median concentration value was below the lower limit of quantitation.
Source: FDA analysis of data from Clinical Study Report Table 15 and Appendix 16.2.5 (individual subject concentration data) from CONRAD A15-137 trial

While TFV-DP concentrations were higher in vaginal tissues at 4 hours post-dose following 14 days of F/TAF administration as compared with F/TDF, it is unclear whether this translates to comparable or higher TFV-DP concentrations beyond 4 hours following 14 days of administration, due to potential (but undetermined) differences in tissue PK between F/TAF and F/TDF. For instance, F/TDF may have a delayed Cmax compared to F/TAF and achieve higher TFV-DP concentrations in mucosal tissues between 4 hours and 24 hours post-dose.

Although the Applicant initially submitted CONRAD A15-137 trial results to support the indication in cisgender women, the applicant did not use the results of CONRAD A15-137 trial to support their claim during the AC meeting. Instead, the Applicant primarily relied on the published clinical EC_{90} value, 40 fmol/million cells of TFV-DP (Anderson et al. 2012) and claimed that Descovy should be effective in cisgender women as EC_{90} value can be quickly achieved (within 2-3 hours) following the administration of Descovy in cisgender women. However, this EC_{90} value was obtained from a previous PrEP trial evaluating Truvada in MSM/TGW. Therefore, it is not clear if this EC_{90} value is relevant for all tenofovir-based PrEP efficacy in all populations given the potential role of mucosal tissues for PrEP. Specifically, 40 fmol/million cells in MSM receiving Truvada is associated with significantly higher rectal tissue concentrations of TFV-DP (> 100 fmol/mg) while 40 mol/million cells in cisgender women receiving DESCOVY is associated with very low (mostly undetectable) levels of TFV-DP in vaginal tissue homogenates.

In summary, the submitted data do not support the expansion of the indication to cisgender women.

<u>Review Question 2: Can HIV PrEP indication be expanded to MSM and TGW adolescents?</u>

The efficacy and safety of Descovy for PrEP have not been evaluated in pediatric subjects, including adolescents. The multidiscipline review team has agreed that extrapolation of efficacy data from the adult PrEP trials to support the indication of PrEP in adolescents is scientifically valid. The biologic

mechanism through which HIV is transmitted and the effects of a drug on that process are expected to be similar between MSM/TGW adults and adolescents. However, no TAF PK data are available following the administration of Descovy in HIV uninfected adolescents. Therefore, the Applicant proposed a two-step approach: 1) demonstrating comparable plasma TAF exposures between HIV infected adults and HIV infected adolescents weighing at least 35 kg following the administration of TAF-containing regimens (e.g., Genvoya) and 2) demonstrating that there is no clinically relevant impact of HIV infection on the PK of TAF.

Based on available TAF PK data in HIV infected adolescents, HIV infected adults, and HIV uninfected adults, the clinical pharmacology review team has concluded that plasma TAF exposures are expected to be comparable between HIV uninfected adults and HIV uninfected adolescents weighing at least 35 kg. Refer to Appendix 4 for the detailed comparison. The use of FTC in adolescents weighing at least 35 kg is supported by the same approach, and it was previously reviewed for the approval of Truvada in adolescent patients. Therefore, the extension of the PrEP indication to adolescents weighing at least 35 kg is acceptable from a clinical pharmacology perspective.

APPENDIX:

Appendix 1: Plasma and Mucosal Tissue Concentrations of TAF and TFV-DP following the administration of F/TAF and F/TDF

Study Title: Exploratory Pharmacokinetic and Pharmacodynamic Study of Oral F/TAF for the Prevention of HIV Acquisition (CONRAD A15-137, (b) (4) , SDN006, 04/02/2019)

Primary Objectives:

- PK: Characterize the PK of oral F/TAF and F/TDF in plasma, PBMCs, cervicovaginal (CV) and rectal fluid, and CV and rectal tissue of healthy premenopausal women
- PD (not discussed in this review due to its exploratory nature):
  - Characterize the anti-HIV activity of F/TAF and F/TDF in CV and rectal fluid
  - Characterize HIV infectivity in CV and rectal tissue at baseline and after treatment with F/TAF and F/TDF

Study Design: This was an external Phase I, open label, parallel PK/pharmacodynamic (PD) study to examine the CV, rectal, PBMC and plasma PK and PD of single and multiple doses of F/TAF and F/TDF conducted by Conrad. There were two phases of this study; the Single Dose Phase followed by the Multiple Dose Phase.

- Single dose
  - F/TAF (200/25 mg) (n = 12)
  - F/TDF (200/300 mg) (n = 12)
- Multiple dose (once daily for 14 days)
  - F/TAF (200/10 mg) (n =24)
  - F/TAF (200/25 mg) (n = 24)
  - F/TDF (200/300 mg) (n = 24)

Although no prior or concomitant medications were restricted, it is not expected that concomitant medications affected the systemic PK of F/TAF or F/TDF. Concomitant medications were reported for 62.5% and 68.0% of participants in the Single and Multiple Dose Phases, respectively, and were similar between treatment groups (58.3% to 66.7% in Single Dose Phase treatment groups; 65.4% to 72.0% in the Multiple Dose Phase treatment groups). In the Multiple Dose Phase, the most frequently reported classes of concomitant medications were anilides (44.0%), vitamins (13.3%), progestogens and estrogens, fixed combinations (10.7%), and selective serotonin reuptake inhibitors (SSRIs) and progestogens and estrogens, sequential preparations (6.7% each).

Samples were collected from plasma, PBMC, rectal and cervicovaginal fluid, and tissue biopsies as shown in the following table:

Table 1: Pharmacokinetic Sampling time

Specimen type (analyte)	**Single Dose Phase**[1] FTC: 200 mg TAF: 25 mg	**Multiple Dose Phase** FTC: 200 mg TAF: 10 or 25 mg		
	Visits 3S – 6S	Visit 2Mb	Visits 3M – 5M	Visits 5M – 8M
	Single dose	First dose (day 1)	Pre-dose troughs	Final dose (Day 14) decay
Plasma[2] (TAF, TFV, FTC)	0.5, 1, 2, 4, 8, 24, 48, and 72h after dose	0.5, 1, 2, 4, and 8h after first MD dose	Days 2, 7 and 14	0.5, 1, 2, 4, 8, 24, 48, and 72h after dose (all participants)
PBMCs (TFV-DP, FTC-TP, dATP, dCTP)	1, 2, 4, 8, 24, 48, and 72h after dose	1, 2, 4, and 8h after first MD dose	Days 2, 7 and 14	1, 2, 4, 8, 24, 48, and 72h after dose (all participants)
CV Tissue[3] (TAF, TFV, FTC, TFV-DP, FTC-TP, dATP, dCTP)	4h after dose			4, 24, and 48h after dose (per site assignment)
CV Fluid (TAF, TFV, FTC)	4h after dose	1, 2, 4, and 8h after first MD dose	Days 2, 7 and 14	4, 8, 24, 48, and 72h after dose (all participants)[5]
Rectal Fluid (TAF, TFV, FTC)				
Rectal Tissue[4] (TAF, TFV, FTC, TFV-DP, FTC-TP, dATP, dCTP)				4h after dose

CV=cervicovaginal; dATP=deoxyadenosine triphosphate; dCTP=deoxycytidine triphosphate; EVMS=Eastern Virginia Medical School; FTC=emtricitabine; FTC-TP=emtricitabine-triphosphate; MD=multiple dose; MWH=Magee-Womens Hospital; PBMCs=peripheral blood mononuclear cells; PD=pharmacodynamic; PK=pharmacokinetics; TAF=tenofovir alafenamide; TFV=tenofovir; TFV-DP=tenofovir-diphosphate.

[1] The Single Dose Phase, and PD assessments in CV tissue in the Multiple Dose phase, were only performed at EVMS.

[2] At Visits 2S (EVMS), 2Ma (EVMS, MWH), and 2Mb (Profamilia), a baseline plasma sample for possible PK assessment was collected.

[3] EVMS collected CV tissue samples for PK at 4 hours, MWH at 24 hours, and Profamilia at 48 hours.

[4] Rectal tissue was only collected at MWH.

[5] CV fluid was not collected at the 8 hour time point at EVMS.

Source: Clinical study report

Reviewer's comments

1. Since TFV-DP is the active metabolite and is the most relevant moiety for the purpose of efficacy extrapolation from Truvada to Descovy in cisgender women, the review focuses on the results of TFV-DP concentrations in tissue and PBMC.

2. Tissue samples were collected at different clinical sites at different time points (e.g., all 4 hour post dose samples were collected at EVMS while all 24 hour post dose samples were collected at MWH). Each subject contributed cervicovaginal tissue samples at only one given timepoint. Therefore, tissue PK parameters (e.g., AUC or Cmax) for an individual subject or correlations between samples collected at different time points cannot be determined

Bioanalysis and OSIS Inspection

Tissue concentrations were analyzed using LC-MS/MS methods using extracts from tissue homogenates. Assuming a tissue density of 1 g/mL, final sample concentrations and the lower limit of quantitation (LLOQ of 0.3 ng/mL) were converted to fmol/g for TFV-DP. PBMC concentrations were analyzed using LC-MS/MS methods. Final TFV-DP concentrations and lower limit of quantitation (LLOQ of 0.200 ng/mL) results were converted to fmol/million cells in PBMC.

Clinical sites and analytical site inspections were conducted by The Office of Study Integrity and Surveillance (OSIS). OSIS inspections concluded that no objectionable conditions were observed, and no Form FDA 483 was issued. However, OSIS has concluded that the data from tissue, peripheral blood mononuclear cells (PBMC), cervicovaginal fluid (CVF), and rectal fluid (RF)samples are acceptable as supportive data, but not pivotal data supporting a regulatory decision, because of the following findings

1) Determination of the recovery of TFV, TFV-dp, FTC, and FTC-tp from tissue was not feasible during the homogenization;
2) Long term and short-term storage stability for TFV, TFV-dp, FTC, and FTC-tp in tissue were not available;
3) For the analysis of TFV-dp, FTC-tp, dATP, and dCTP in PBMC samples, the site did not report the acceptance criteria of accuracy correctly for standards and QCs;
4) For the analysis of TFV-dp and FTC-tp in PBMC samples, performance of analytical runs was not monitored using QCs prepared in the same matrix as subject samples;
5) The site could not obtain blank matrix of cervicovaginal fluid and rectal fluid, thus has no data demonstrating parallelism between the cervicovaginal fluid/rectal fluid and saliva, which was used as a surrogate matrix;
6) Cervicovaginal fluid and rectal fluid samples were collected using MeroCels sponge; however, the recovery of TAF, TFV, and FTC from MeroCel sponge during the extraction process is unknown;
7) Stability data for TAF, TFV, and FTC in CVF or RF are not available.

Please see OSIS reviews conducted by Dr. Zhang (7/23/2019), Dr. Cai and Dr. Gupta (7/23/2019), for details.

PK Results

Mucosal Tissue TFV-DP Concentrations:

Following single dose administration of Descovy or Truvada, 83% of vaginal tissue samples were below the lower limit of quantitation (BLQ) at 4 hours. Following 14-day administration of Descovy, median TFV-DP concentrations in vaginal tissues were 3-fold above the lower limit of quantitation (LLOQ) at 4 hours after the last dose. In contrast, 62% (5/8) of vaginal tissue samples were BLQ at this same time point following 14-day administration of Truvada. In both treatment groups, TFV-DP concentrations were mostly (70-80%) BLQ at 24 hours and 48 hours post-dose following 14 days of administration. Results for cervical tissue samples were largely consistent with those for vaginal tissues.

It is unclear if the results at 4 hours translates to comparable or higher TFV-DP concentrations beyond 4 hours following 14-day administration of Descovy. In rectal tissue, more than 10-fold of TFV-DP concentrations were observed following F/TDF administration as compared to F/TAF.

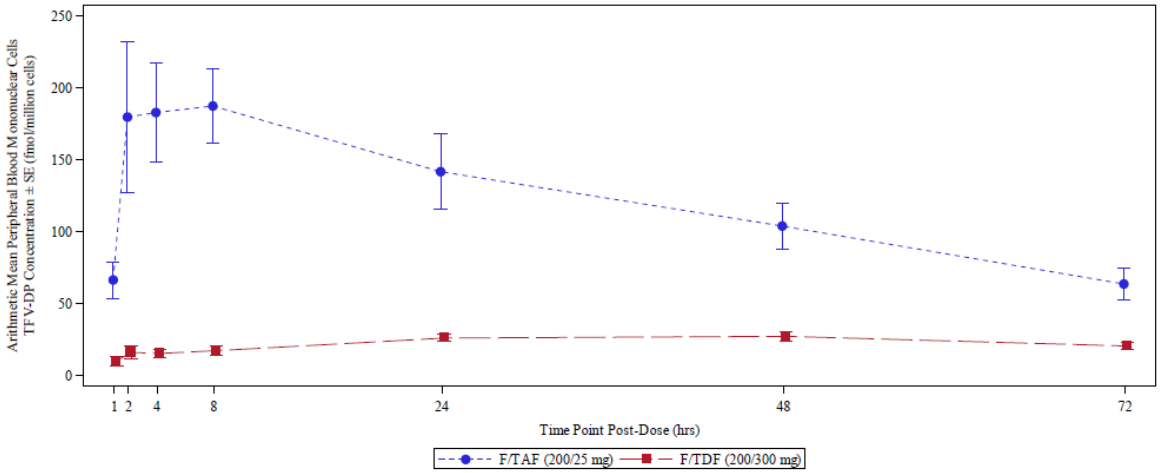
Table 2: Mucosal Tissue TFV-DP Concentrations Following 14 days of administration of F/TAF 200/25 mg and F/TDF 200/300 mg

		Vaginal tissue		Cervical tissue		Rectal tissue	
		F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF
4 hours	% BLQ*	0% (0/8)	62% (5/8)	25% (2/8)	88% (7/8)	31% (9/29)	3% (1/30)
	Median TFV-DP† (fmol/mg)	151	N/A	126	N/A	150	2,521
24 hours	% BLQ*	80% (12/15)	69% (11/16)	67% (10/15)	81% (13/16)	Not Collected	
	Median TFV-DP† (fmol/mg)	N/A	N/A	N/A	N/A		
48 hours	% BLQ*	80% (12/15)	79% (11/14)	93% (14/15)	100% (14/14)		
	Median TFV-DP† (fmol/mg)	N/A	N/A	N/A	N/A		

PBMC TFV-DP Concentrations:

Median TFV-DP concentrations were 6- to 8-fold higher in PBMC following single or multiple doses of F/TAF 200/25 mg compared to F/TDF 200/300 mg. There were about a 5-fold accumulation of TFV-DP following 14-days of administration of both F/TAF and F/TDF. Tmax was highly variable, particularity for F/TDF, because of a flat concentration-time profile. Therefore, it is hard to determine if F/TAF and F/TDF reaches Cmax at the same time.

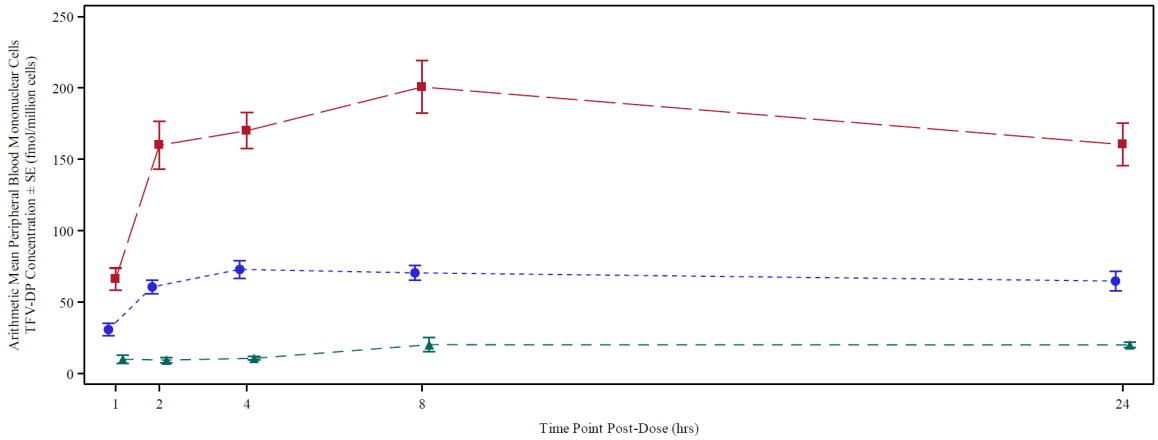
Figure 1: PBMC Mean TFV-DP Concentrations over Time – Single dose Phase



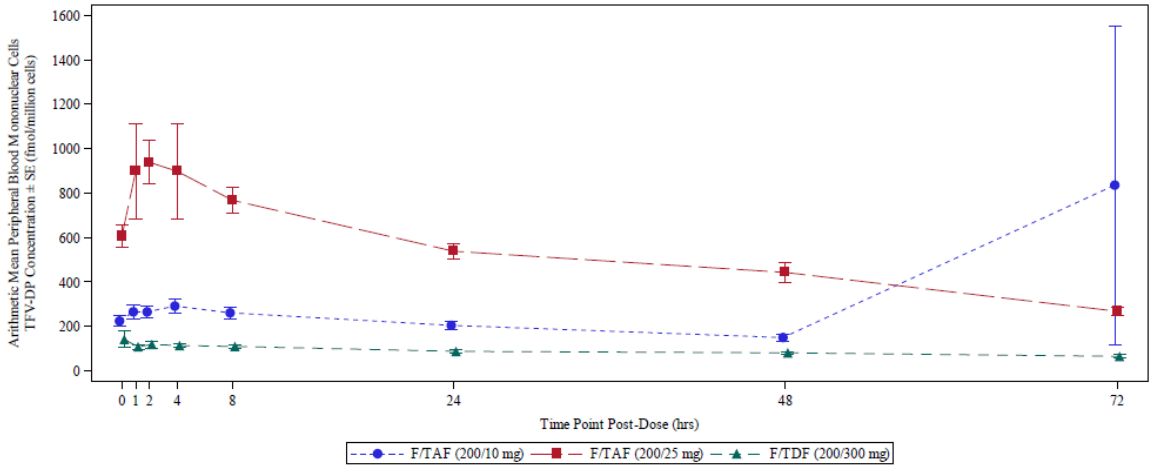
Note: Concentrations below LLOQ were imputed as 0.5 * LLOQ.
Source: Study Report

Figure 2: PBMC Mean TFV-DP Concentrations over Time – Multiple dose Phase

Day 1



Day 14



Note: Mean analyte concentrations with F/TAF (200/10 mg) at 72 hours following 14 days of administration were artificially elevated due to an outlier (low) PBMC cell count in one participant (b) (6)).
Note: Concentrations below LLOQ were imputed as 0.5 * LLOQ.
Source: Study Report

Table 3: PBMC Median TFV-DP PK Parameters

Median TFV-DP PK Parameters in PBMC	Multiple Dose Phase Median (Range)			Single Dose Phase Median (Range)	
	After 14 Daily Doses of F /TAF 200/25 mg (N=24)	After 14 Daily Doses of F/TDF 200/300 mg (N=25)	After 1 Dose of F/TAF 200/25 mg (N=24)	After Single Dose of F/TAF 200/25 mg (N= 12)	After Single Dose of F/TDF 200/300 mg (N= 12)
AUC_{0-24h} (h•fmol/million cells)	15,214.8 (8700.0, 42,688.6)	2497.5 (561.7, 3993.1)	3781.1 (2058.4, 8287.5)	3503.9 (1564.9, 10009.4)	429.9 (180.4, 842.0)
Cmax (fmol/million cells)	1020.9 (439.5, 5725.8)	139.2 (26.2, 999.9)	195.2 (116.8, 440.3)	184.1 (79.9, 740.7)	33.3 (12.5, 59.7)
Tmax (h)	4 (1, 72)	2 (1, 48)	8 (2, 24)	4 (2, 8)	24 (2, 72)
C_{24h} (fmol/million cells)	523.2 (272.9, 931.3)	86.7 (25.0, 141.5)	Not determined	Not determined	Not determined

TAF and TFV concentrations in plasma were consistent with those previously observed in healthy subjects. TAF was undetectable in vaginal and rectal fluid. TFV AUC_{0-24h} was about 9- to 10-fold higher for F/TDF than F/TAF in rectal fluid and cervicovaginal fluid. Plasma and tissue concentrations of FTC and FTC-TP following the administration of Descovy or Truvada are consistent with previously reported results and there were no differences between F/TDF and F/TAF.

Conclusion:

- The tissue concentration results from this study are not sufficient to support the PrEP indication because most of the cervicovaginal tissue samples were unquantifiable.

Appendix 2: PK Summary of DISCOVER trial

DISCOVER trial is a Phase 3, randomized, double-blind study to evaluate the safety and efficacy of F/TAF fixed-dose combination once daily for PrEP in men and transgender women who have sex with men and are at risk of HIV-1 infection. Eligible participants were randomized in a 1:1 ratio to 1 of the following 2 treatment groups:

Treatment Arm 1: Descovy (F/TAF 200/25 mg) FDC + placebo-to-match Truvada (n = 2500)
Treatment Arm 2: Truvada (F/TDF 200/300 mg) FDC + placebo-to-match Descovy (n = 2500)

FTC and TFV in plasma PK samples, and FTC-TP and TFV-DP in PBMC PK samples from F/TAF and F/TDF groups were analyzed and evaluated at Week 4 (trough concentrations) in a subset (planned: ~ 10%) of participants, as well as for all participants diagnosed with HIV infection.

Mean plasma trough concentrations (Ctau) of TFV were 84% lower for F/TAF as compared to F/TDF. Mean plasma FTC Ctau was similar between the 2 groups. In PBMCs, the mean TFV-DP Ctau was 6.3-fold higher in participants with F/TAF versus F/TDF, and mean FTC-TP Ctau was similar between the 2 groups. The results were consistent with the known PK of F/TAF and F/TDF.

Table 4: Summary and Statistical Comparisons of TFV, FTC, TFV-DP and FTC-TP PK Parameters

Mean (%CV) PK Parameter (Biomatrix)	F/TAF (Test)	F/TDF (Reference)	GLSM Ratio% (90% CI) (Test/ Reference)
TFV (plasma)	N = 164	N = 160	
Ctau (ng/mL)	9.4 (73.9)	62.6 (71.7)	15.74 (14.02,17.68)
FTC (plasma)	N = 160	N = 160	
Ctau (ng/mL)	150.5 (201.0)	141.8 (206.8)	100.06 (85.60,116.95)
TFV-DP (PBMC)	N = 158	N = 151	
Ctau (fmol/million cells)	728.9 (156.8)	157.5 (234.2)	630.60 (514.44,772.99)
FTC-TP (PBMC)	N = 152	N = 145	
Ctau (fmol/million cells)	11016.4 (102.5)	9258.7 (94.8)	109.18 (92.09,129.44)

Appendix 3: Pooled Data to Demonstrate No Clinically Significant Difference between Gender or HIV-1 infection status for TAF

The applicant provided pooled plasma exposures of TAF, and PBMC-associated TFV-DP from female and male volunteers in multiple-dose, Phase 1 studies following administration of Descovy, Genvoya, Biktarvy, or Vemlidy, as well as pooled plasma exposures of TAF, and PBMC-associated TFV-DP from women with HIV-1 in Phase 2 and Phase 3 studies following administration of Genvoya or Biktarvy, to support extrapolation of efficacy data from Study GS-US-412-2055 to cisgender women for PrEP indication.

Table 5: Summary and Statistical Comparison of TAF Plasma Pharmacokinetic Parameters between Women and Men Volunteers

	Mean (%CV) Min, Max		
TAF PK Parameter	**Women (N = 138)**	**Men (N = 161)**	**% GLSM Ratio (90% CI)**
AUC_{tau} (h•ng/mL)[a]	338.5 (34.9) 142.4, 835.6	255.9 (37.4) 101.9, 659.0	135.57 (126.54, 145.23)
C_{max} (ng/mL)	313.3 (65.9) 63.2, 1510.0	237.8 (59.4) 58.2, 814.0	123.81 (112.07, 136.77)

The estimates and 90% CI were from an ANCOVA model adjusted by Study ID.
Data were pooled from the following multiple-dose, Phase 1 PK studies: Studies GS-US-180-4149, GS-US-292-0101, GS-US-292-0103, GS-US-292-0108, GS-US-292-1316, GS-US-311-0101, GS-US-342-1167, GS-US-367-1657, GS-US-380-1761, GS-US-380-1999, and GS-US-380-4017
a N = 133 women; N = 160 men for AUC_{tau}
Source: Applicant's Extrapolation Report for Women

Table 6: Summary of PBMC-Associated TFV-DP Pharmacokinetic Parameters for Women and Men Volunteers

TFV-DP PK Parameter	Mean (%CV) Min, Max	
	Women (N = 42)	Men (N = 13)
AUC_{tau} (h•fmol/million cells)	16,416.8 (90.3) 3311.4, 56,803.7	10,040.8 (46.3) 4732.2, 19,406.1
C_{tau} (fmol/million cells)	353.2 (122.9) 6.7, 1889.7	377.9 (48.4) 187.4, 706.7

Data were pooled from the following multiple-dose, Phase 1 PK studies: Studies GS-US-180-4149 and GS-US-380-4017
Source: Applicant's Extrapolation Report for Women

Table 7: Summary and Statistical Comparison of TAF Plasma Pharmacokinetic Parameters between Female Volunteers and Women with HIV-1

TAF PK Parameter	Mean (%CV) Min, Max		% GLSM Ratio (90% CI)
	Female Volunteers (N = 138)	Women with HIV-1 (N = 169)	
AUC_{tau} (h•ng/mL)[a]	338.5 (34.9) 142.4, 835.6	226.5 (132.1) 51.7, 3337.4	176.33 (161.26,192.81)
C_{max} (ng/mL)	313.3 (65.9) 63.2, 1510.0	158.5 (50.7) 21.1, 569.9	190.94 (173.10,210.63)

The estimates and 90% CI were from an ANOVA model.
Data from female volunteers were pooled from the following multiple-dose, Phase 1 PK studies: GS-US-180-4149, GS-US-292-0101, GS-US-292-0103, GS-US-292-0108, GS-US-292-1316, GS-US-311-0101, GS-US-342-1167, GS-US-367-1657, GS-US-380-1761, GS-US-380-1999, and GS-US-380-4017
Data from women with HIV-1 were pooled from the following Phase 2 and Phase 3 studies: GS-US-292-0102, GS-US-292-0104, GS-US-292-0109, GS-US-292-0111, GS-US-380-1489, and GS-US-380-1490
a N = 133 female volunteers for AUC_{tau}
Source: Applicant's Extrapolation Report for Women

Reviewer's Assessment
While we agree that there is no clinically significantly difference in TAF plasma concentrations or TFV-DP concentrations in PBMC between males and females, we disagree that this information alone is enough to support the extrapolation of efficacy. Refer to the Question-Based Review.

Appendix 4: Pooled Data to Demonstrate No Clinically Significant Difference on TAF Exposures between Adolescents with HIV-1 and Adults with HIV-1 or between Adult Volunteers and Adults with HIV-1 for TAF

Descovy is currently approved in pediatric patients weighing at least 35 kg for HIV treatment based on PK, safety, and efficacy data from patients receiving F/TAF in combination with elvitegravir and cobicistat (Genvoya). In addition, there are PK, safety, and efficacy data from patients receiving F/TAF in combination with bictegravir (Biktarvy).

To support the extension of the PrEP indication to adolescents, the Applicant proposed an extrapolation approach, demonstrating comparable plasma TAF concentrations between HIV uninfected adults and

adolescents weighing at least 35 kg. Since there are no TAF PK data in HIV uninfected adolescents, the Applicant proposed a two-step approach; demonstrating comparable plasma TAF exposures between HIV infected adults and adolescents weighing at least 35 kg and demonstrating that there is no clinically relevant impact of HIV infection on the PK of TAF.

Following the administration of Genvoya, comparable AUC, but approximately 40 % lower Cmax, were observed in HIV infected adolescents as compared to HIV infected adults (Table 8). The difference in Cmax is likely driven by variability rather than a true difference between the two populations. Following the administration of Biktarvy, there was no difference in Cmax of TAF between adult patients and adolescent patients (Biktarvy USPI). In addition, popPK analyses for TAF of Genvoya and Biktarvy indicated that age and weight were not significant covariates.

Table 8: Summary and Statistical Comparison of TAF Plasma PK Parameters in Adolescents with HIV-1 Versus Adults with HIV-1 Treated with Genvoya

TAF PK Parameter	Mean (%CV) Min, Max		% GLSM Ratio (90% CI)
	Adolescents[a] (N = 46)	Adults[b] (N = 539)	
AUC_{tau} (h•ng/mL)	195.3 (48.2) (68.6, 464.9)	206.4 (71.8) (47.2, 1869)	97.09 (85.33, 110.46)
C_{max} (ng/mL)	92.3 (68.2) (14.0, 263.2)	162.2 (51.1) (19.7, 968.2)	50.42 (42.17, 60.29)

a PK parameters for adolescents were population PK parameters from Cohort 1 participants in Study GS-US-292-0106 (QP-2018-1027 TAF TFV HIV Pediatric Pop PK).
b PK parameters for adult population were population PK parameters from Studies GS-US-292-0104 and GS-US-292-0111 {GENVOYA® 2019}.
The estimates and 90% CI were from an ANOVA model.
Source: Applicant's Extrapolation Report for Adolescents

The Applicant compared Cmax and AUC of TAF between HIV uninfected adults (adult volunteers) and HIV adult patients (Table 9). While Cmax and AUC of TAF are approximately 60% higher in HIV uninfected adults and HIV infected adults this is not considered clinically relevant for safety.

Table 9: Summary and Statistical Comparisons of TAF Plasma PK Parameters in Adult Volunteers Versus Adults with HIV-1 Treated with Descovy, Genvoya, Biktarvy, and Vemlidy

TAF PK Parameter	Mean (%CV) Min, Max		% GLSM Ratio (90% CI)
	Adult Volunteers (N = 299)	Adults with HIV-1 (N = 1362)	
AUC_{tau} (h•ng/mL)	293.4 (38.9)[a] (101.9, 835.6)	185.8 (85.5) (24.5, 3337.4)	157.90 (150.40, 165.78)
C_{max} (ng/mL)	272.6 (65.3) (58.2, 1510.0)	146.7 (50.2) (19.5, 1281.9)	165.83 (157.85, 174.21)

a N = 293
The estimates and 90% CI were from an ANCOVA model.
Source: Applicant's Extrapolation Report for Adolescents
Adult volunteers: TAF PK parameters were pooled from Phase 1 studies of Descovy, Genvoya, Biktarvy, and Vemlidy
Adults with HIV-1: TAF PK parameters were determined using data from Phase 2 and Phase 3 studies of Genvoya and Biktarvy

Reviewer's Assessment

Overall, the proposed approach and the submitted data support extension of the indication to adolescent patients. The use of FTC in adolescents weighing at least 35 kg is supported by the same approach, and it was previously reviewed for the approval of Truvada in adolescent patients.

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/s/

HUIMIN ZHENG
09/12/2019 05:01:48 PM

SU-YOUNG CHOI
09/12/2019 05:04:42 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208215Orig1s012

<u>OTHER REVIEW(S)</u>

Division of Antiviral Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 208215/S12

Name of Drug: DESCOVY® (emtricitabine and tenofovir alafenamide), 200/25 mg tablet

Applicant: Gilead Sciences Inc.

Labeling Reviewed

Submission & Receipt Date: Supplemental Application S12 received April 5, 2019

Background and Summary Description:

DESCOVY® is a two-drug fixed-dose combination (FDC) tablet consisting of emtricitabine and tenofovir alafenamide (F/TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTLs) and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults (b) (4) [redacted].

On April 8, 2016, Gilead Sciences Inc. (Gilead) submitted an Investigational New Drug Application to serve as the registrational application to support the use of F/TAF for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in uninfected individuals at high risk, a new indication for DESCOVY®. Study GS-US-412-2055 (DISCOVER) is a single, randomized, double-blind, active-controlled, non-inferiority trial conducted in adult MSM comparing the safety and efficacy of DESCOVY® to approved Truvada. This trial will serve as the pivotal trial to support the PrEP indication. Throughout the development program, the Division provided guidance on study design and analytical methods for the primary endpoint of the ongoing DISCOVER trial.

On November 29, 2018 a pre-sNDA meeting was held via a teleconference wherein the content and format of the planned sNDA was discussed. Gilead provided an overview of their planned bridging strategy to support a PrEP indication for DESCOVY® in at-risk women. The strategy included submission of information from external preclinical studies in relevant non-human primate models (Massud et al, CROI 2018; Schwartz et al [CONRAD, data on file]) and external pharmacokinetic (PK) studies in healthy female volunteers (Cottrell et al, 2017; Schwartz et al, HIVR4P 2018). The bridging strategy will also rely on safety, PK and efficacy data from Gilead-sponsored clinical trials of F/TAF in both men and women (HIV-uninfected and HIV-infected). The Division noted that complete study report and datasets from the multiple-dose PK trial in healthy women (Schwartz et al) should be submitted to support the sNDA, as the Division considers steady-state PK data from the female genital tract to be critical to the bridging strategy for at-risk

women.

On April 5, 2019, Gilead submitted the aforementioned sNDA. In this supplement the Applicant proposes a PrEP indication for DESCOVY® to be consistent with that approved for Truvada; to reduce the risk of HIV infection in at-risk adults and adolescents. As the effectiveness of DESCOVY® for PrEP has not been clinically evaluated in women or adolescents, the Division is bringing this application to an Advisory Committee Meeting to solicit feedback on the Applicant's strategy to support approval of the PrEP indication in women and adolescent girls.

The Advisory Committee Meeting was held on August 7th , 2019, the results of the meeting were as follows:

- Has the Applicant provided substantial evidence of the safety and effectiveness of Descovy® for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually-acquired HIV-1 infection in men and transgendered women who have sex with men?
    - Vote Result: Yes: 16 No: 2 Abstain: 0
- Do the data from the DISCOVER trial, in combination with the available pharmacokinetic data and other previous HIV-1 prevention trials with Truvada® in cisgender women, allow for the expansion of the Descovy® PrEP indication to include cisgender women?
    - Vote Result: Yes: 8 No: 10 Abstain: 0
- Please discuss whether the data from the DISCOVER trial are relevant to at risk men who practice insertive vaginal sex with cisgender women.
    - There was an overall agreement that the data might be suggestive of efficacy, but that more studies should be conducted to better understand the potential benefits.

Supplement 011- is currently under review for the addition of Postmarketing Experience subsection to the ADVERSE REACTIONS section; this change was incorporated in S012's approval.

Review

- Gilead's USPI submitted on September 27, 2019 (latest proposed labeling)
- Last approved labeling was an efficacy supplement (NDA 208215 S005) approved on 09/28/2017
- The primary purpose of this efficacy supplement was to allow for the use of DESCOVY in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating DESCOVY for HIV-1 PrEP.

GLOBAL EDITS • Edits Supported by data from the DISCOVER TRIAL as described below.

• Minor editorial and formatting revisions were made throughout the Prescribing Information (PI) and Med Guide including the approved revision date and numerical changes to the table numbers and labeling subsections
• Changes from patients to individuals throughout the PI
• The Patient Package Insert was changed to a Med Guide to align with approved TRUVADA USPI
• Inclusion of NCT trial numbers throughout section 14
• For each Recent Major Changes listed in the highlights, the corresponding text in the Full Prescribing Information is marked with a vertical line on the left edge per labeling regulations:
  o Black Box Warning
  o Indications and Usage: 1.2: HIV-1 PrEP
  o Dosage and Administration:
  ▪ 2.1, 2.3, 2.5 Revisions to include HIV PrEP
  ▪ 2.2: HIV-1 Screening for Individuals Receiving DESCOVY for HIV-1 PrEP
  ▪ 2.4: Recommended Dosage for HIV-1 PrEP in Adults and Adolescents Weighing at Least 35 kg
  o Contraindications: DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status
  o Warnings and Precautions
  ▪ 5.2: Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When DESCOVY Is Used for HIV-1 PrEP

HIGHLIGHTS OF PRESCRIBING INFORMATION

- Black Box Warning: Addition of HIV PrEP information
- RECENT MAJOR CHANGES:
  - Black Box Warning
  - Indications and Usage: 1.2: HIV-1 PrEP
  - Dosage and Administration:
    - 2.1, 2.3, 2.5 Revisions to include HIV PrEP
    - 2.2: HIV-1 Screening for Individuals Receiving DESCOVY for HIV-1 PrEP
    - 2.4: Recommended Dosage for HIV-1 PrEP in Adults and Adolescents Weighing at Least 35 kg
  - Contraindications: DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status
  - Warnings and Precautions
    - 5.2: Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When DESCOVY Is Used for HIV-1 PrEP
    - Removal of changes that were highlighted from S5 as it is more than one year since the change:
- INDICATIONS AND USAGE:
  - 1.2: HIV 1 PrEP new indication and Limitations of Use Statement
- DOSAGE AND ADMINISTRATION:
  - 2.1: Testing When Initiating and During Use of DESCOVY for Treatment of HIV-1 Infection or for HIV-1 PrEP
  - 2.2: HIV-1 Screening for Individuals Receiving DESCOVY for HIV-1 PrEP
  - 2.4: Recommended Dosage for HIV-1 PrEP in Adults and Adolescents Weighing at Least 35 kg
  - 2.5: Not Recommended in Individuals with Severe Renal Impairment for Treatment of HIV-1 Infection or for HIV-1 PrEP
- CONTRAINDICATIONS:
  - DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status
- WARNINGS AND PRECAUTIONS
  - 5.2: Comprehensive management to reduce the risk of sexually transmitted infections (STIs), including HIV-1, when DESCOVY is used for HIV-1 PrEP: Counsel on adherence to daily dosing and safer sex practices, including condoms, to reduce the risk of STI
  - 5.2: (b) (4) [redacted]
- ADVERSE REACTIONS
  - 6.1: In HIV-1 uninfected adults in a PrEP trial, the most common adverse reaction (incidence greater than or equal to 5%, all grades) was diarrhea
- USE IN SPECIFIC POPULATIONS
  - 8.4: Treatment of HIV-1 Infection: (b) (4) [redacted]
  - 8.4: HIV-1 PrEP: Not recommended for individuals weighing less than 35 kg

FULL PRESCRIBING INFORMATION: CONTENTS

- WARNING addition
  - Risk of Drug Resistance with use of DESCOVY for HIV-1 PrEP in undiagnosed early HIV-1 Infection
- INDICATIONS AND USAGE:
  - 1.1 (only because a new indication was added): Treatment of HIV-1 Infection
  - 1.2: HIV-1 Pre-Exposure Prophylaxis (PrEP)
- DOSAGE AND ADMINISTRATIONS:
  - 2.1, 2.3, 2.5 Revisions to include HIV PrEP information
  - 2.4: Recommended Dosage for HIV-1 PrEP in Adults and Adolescents Weighing at Least 35 kg
  - 2.5: Not Recommended in Individuals with Severe Renal Impairment for Treatment of HIV-1 Infection or for HIV-1 PrEP
- WARNINGS AND PRECAUTIONS:
  - 5.2: Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When DESCOVY Is Used for HIV-1 PrEP
- ADVERSE REACTIONS
  - 6.2: Post Marketing Experience
- CLINICAL STUDIES
  - 14.1 Overview of Clinical Trials
  - 14.2 Clinical Trial Results for Treatment of HIV-1
  - 14.3 Clinical Trial Results for HIV-1 PrEP

FULL PRESCRIBING INFORMATION

- Black Box Warning: Addition of HIV PrEP information
- INDICATIONS AND USAGE:
  - 1.2: HIV 1 PrEP new indication
  - Limitations of Use Statement: The indication does not include use of DESCOVY in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated
- DOSAGE AND ADMINISTRATION
  - 2.1, 2.3, 2.5: Revisions to include information for HIV-1 PrEP
  - 2.2, 2.4: Addition of HIV-1 screening information for HIV PrEP patients and recommended dosage for HIV-1 PrEP
- CONTRAINDICATIONS:
  - DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status
- WARNINGS AND PRECAUTIONS
  - 5.2: Addition of recommendations for the Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When DESCOVY Is Used for HIV-1 PrEP
- ADVERSE REACTIONS
  - 6.1: Addition of safety information to subsection Adverse Reactions from Clinical Trial Experience in HIV-1 Uninfected Individuals Taking DESCOVY for HIV-1 PrEP
  - 6.1: Bone Mineral Density Effects subsection removed fracture information
  - 6.2: Post Marketing Experience: addition of Angioedema, urticaria, and rash as proposed with S11
- USE IN SPECIFIC POPULATIONS
  - 8.1: Revisions to Risk Summary to align with PLLR
  - 8.1: Addition of Human Data Information for Tenofovir Alafenamide to align with PLLR and update APR data
  - 8.4: Addition of HIV-1 PrEP Pediatric Use data (adolescents weighing at least 35kg)
- CLINICAL PHARMACOLOGY
  - 12.3: Addition of PK information for pediatric patients for HIV-1 PrEP
  - 12.4: Addition of Prophylactic Activity in a Nonhuman Primate Model of HIV-1 Transmission
  - 12.4: Addition of Resistance information for HIV-1 PrEP
- CLINICAL STUDIES
  - Clinical Overview added with all DESCOVY Trials completed with NCT numbers
  - 14.3: Newly Added clinical trial results for HIV-1 PrEP
- HOW SUPPLIED/STORAGE AND HANDLING
  - Addition of information to Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).
- PATIENT COUNSELING INFORMATION
  - Addition of Important Information for Uninfected Individuals Taking DESCOVY for HIV-1 PrEP

MED GUIDE

- Patient Package Information was converted to a MED GUIDE by Application to align with TRUVADA USPI. The MED GUIDE reflects changes made to the USPI

Recommendations

The changes proposed by the applicant are acceptable and an approval letter will be sent. Please see the clinical review, clinical pharmacology, clinical microbiology, and biometrics review for additional information.

Alicia Moruf	Please refer to electronic signature date
Regulatory Project Manager	Date
Karen Winestock	Please refer to electronic signature date
Chief, Project Management Staff	Date

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KAREN D WINESTOCK
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 12, 2019
To:	Debra Birnkrant, MD Director **Division of Antiviral Products (DAVP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	DESCOVY (emtricitabine and tenofovir alafenamide)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208215
Supplement Number:	S-012
Applicant:	Gilead Sciences, Inc.

1 INTRODUCTION

On April 5, 2019, Gilead Sciences, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 208215/S-012 for DESCOVY (emtricitabine and tenofovir alafenamide) tablets. With this supplement, the Applicant proposes changes to the approved Prescribing Information (PI) to include a new indication of Pre-exposure Prophylaxis (PrEP) of HIV-1 infection in at-risk adults and adolescents weighing at least 35 kg. In addition, the Applicant proposes changes to include revisions to section 8.1 Pregnancy and section 8.2 Lactation to align with the Pregnancy and Lactation Labeling Rule (PLLR). The Applicant has converted the Patient Package Insert (PPI) to a Medication Guide (MG) with the proposal of the new indication for PrEP.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on May 2, 2019 for DMPP and OPDP to review the Applicant's proposed MG for DESCOVY (emtricitabine and tenofovir alafenamide) tablets.

2 MATERIAL REVIEWED

- Draft DESCOVY (emtricitabine and tenofovir alafenamide) tablets MG received on April 5, 2019, and received by DMPP and OPDP on September 3, 2019.
- Draft DESCOVY (emtricitabine and tenofovir alafenamide) tablets Prescribing Information (PI) received on April 5, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 3, 2019.
- Approved DESCOVY (emtricitabine and tenofovir alafenamide) tablets labeling dated December 20, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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WENDY R LUBARSKY
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SHARON R MILLS
09/12/2019 12:15:12 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 12, 2019

To: Alicia Moruf, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for DESCOVY (emtricitabine and tenofovir alafenamide) tablets, for oral use

NDA: 208215 / S-012

In response to DAVP consult request dated May 2, 2019, OPDP has reviewed the proposed product labeling (PI), and Medication Guide for DESCOVY (emtricitabine and tenofovir alafenamide) tablets, for oral use (Descovy). This supplement (S-012) proposes changes to the approved PI to include a new indication of Pre-exposure Prophylaxis (PrEP) of HIV-1 infection in at-risk adults and adolescents weighing at least 35 kg. In addition, the Applicant proposes changes to include revisions to section 8.1 Pregnancy and section 8.2 Lactation to align with the Pregnancy and Lactation Labeling Rule (PLLR). The Applicant has converted the Patient Information (PPI) to a Medication Guide with the proposal of the new indication for PrEP.

PI / Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DAVP (Alicia Moruf) on September 3, 2019, and we have no comments on the PI.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on September 12, 2019.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov .

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WENDY R LUBARSKY
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Clinical Inspection Summary

Date	8/30/2019
From	Karen Bleich, M.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Myung-Joo Patricia Hong, Regulatory Project Manager William Tauber, M.D., Clinical Reviewer Division of Anti-Viral Drug Products
NDA/BLA #	NDA 208215/S012
Applicant	Gilead Sciences, Inc
Drug	Descovy (emtricitabine/tenofovir alafenamide) fixed-dose combination tablets
NME (Yes/No)	No
Therapeutic Classification	Priority review
Proposed Indication(s)	Pre-exposure prophylaxis to reduce risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg
Consultation Request Date	5/2/2019
Summary Goal Date	9/5/2019
Action Goal Date	10/5/2019
PDUFA Date	10/5/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study GS-US-412-2055 were submitted to the Agency in support of supplement 12 for NDA 218215 to expand the indication for Descovy to include pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1. Three clinical sites from the study were selected for audit: Dr. Edwin DeJesus (Site 698), Dr. Peter Ruane (Site 407), and Dr. Jay Gladstein (Site 12936). The sites selected were among the highest enrollers of study subjects, and thus contributed significantly to the overall efficacy determination. On-site inspections demonstrated no significant findings at any of the audited sites related to data integrity or human subject protection.

The data from Study GS-US-412-2055 submitted to the Agency in support of the NDA appear reliable based on the available information and the conduct of the study appears to have included appropriate protection of the rights and welfare of the human research subjects.

II. BACKGROUND

Gilead Sciences, Inc. seeks approval to market Descovy for pre-exposure prophylaxis to reduce risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg. This request is based on the results of one Phase 3 Study, summarized below:

Study
GS-US-412-2055: "A Phase 3, randomized, double-blind study to evaluate the safety and efficacy of emtricitabine and tenofovir alafenamine fixed-dose combination (Descovy) once daily for pre-exposure prophylaxis in men and transgender women who have sex with men and are at risk of HIV-1 infection"

Number of subjects
5399

Number of sites
94 sites in the United States, Canada, Austria, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, and the United Kingdom

Study dates
September 2nd, 2016 – January 31st, 2019

Primary Objective
To assess the rates of HIV-1 infection in men and transgender women who have sex with men who are administered daily Descovy or Truvada with a minimum follow-up of 48 weeks and at least 50% of participants had 96 weeks of follow-up after randomization.

Primary Efficacy Endpoint
Incidence of HIV-1 infection per 100 person-years in the FAS, assessed when all participants had a minimum follow-up of 48 weeks and at least 50% of participants had 96 weeks of follow-up, or had permanently discontinued from the study.

III. RESULTS (by site):

1. Dr. Edwin DeJesus, M.D., Orlando, Florida (Site 698)
The site screened 325 subjects and enrolled 306 subjects. At the time of the inspection, the study was still ongoing but closed to enrollment.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, informed consent, site monitoring, investigational product accountability, and financial disclosures.

A comprehensive review of the source document records for 30 enrolled subjects was performed, including primary endpoint HIV test results, secondary endpoint hip bone density

results, study drug administration, adverse events, and medical history. The source data was compared to the data listings submitted to the application.

No significant inconsistencies or deficiencies were identified at the site.

2. Dr. Peter Ruane, M.D., Los Angeles, California (Site 407)
The site screened 504 subjects and enrolled 456 subjects. At the time of the inspection, the open label phase of the study was beginning.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, informed consent, site monitoring, investigational product accountability, and financial disclosures. Significant financial disclosures at the site are consistent with documentation submitted in the NDA submission (Section 1.3.4 Financial Certification and Disclosure). The inspection also included a review of electronic records and electronic signatures.

A comprehensive review of the source document records for 30 enrolled subjects was performed, including consent, entry criteria, randomization, primary endpoint data, protocol compliance, and adverse events. Additionally, source documents were reviewed for all subjects who tested positive for HIV and all discontinued subjects. The source data was compared to the data listings submitted to the application

No significant inconsistencies or deficiencies were identified at the site.

3. Dr. Jay Gladstein, M.D., Los Angeles, California (Site 12936)
The site screened 169 subjects and enrolled 155 subjects. At the time of the inspection, the study was still ongoing.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, informed consent, site monitoring, investigational product accountability, laboratory certifications, and financial disclosures.

A comprehensive review of the source document records for 46 enrolled subjects was performed, including primary and secondary efficacy endpoints, adverse events, protocol deviations, randomization assignments, subject discontinuations, laboratory results, and concomitant medications. The source data was compared to the data listings submitted to the application.

The inspection identified the following deficiencies:

- Incorrect dispensing of study drug/placebo (3 instances involving Subjects (b) (6), (b) (6), and (b) (6))
    - The dispensing errors were determined to be caused by human error. Subject (b) (6) returned the incorrect drug product and did not ingest any incorrect drug product. Subject (b) (6) incorrectly took a total of 4 doses of placebo before the error was corrected. Subject (b) (6) took a total of 13 doses of active drug product before the error was corrected. None of the subjects

became HIV positive during the study. Both cases of subjects receiving and ingesting incorrect drug product are reported in the NDA submission as protocol deviations.

- Failure to obtain results of rapid HIV testing prior to randomization and dosing (17 subjects)
  - The subjects had off-site HIV testing instead of rapid (same day) HIV testing. The subjects all tested HIV negative but were incorrectly enrolled prior to determination of their HIV status.
- Failure to dispense medication to a single subject at the subject's week 12 visit
  - The subject subsequently discontinued participation in the study and is reported in the NDA submission as a subject discontinuation.

A response letter from the CI dated 07/22/2019 indicated that the site took voluntary corrective actions (prior to the inspection) including establishing new Standard Operation Procedures for medication dispensing and contracting with a new site management company. The CI instituted additional quality control measures in response to the inspection.

The lack of sufficient quality control measures during the study appear to have been adequately addressed by the CI. The deficiencies identified at the site do not significantly impact the integrity of the study data.

{See appended electronic signature page}

Karen Bleich, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.
Review Division /Division Director/Debra Birnkrant
Review Division /Medical Team Leader/Wendy Carter
Review Division /Project Manager/Myung Joo Hong
Review Division/MO/William Tauber
OSI/Office Director/David Burrows
OSI/DCCE/ Division Director/Ni Aye Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Karen Bleich
OSI/ GCP Program Analysts/Yolanda Patague/Joseph Peacock
OSI/Database PM/Dana Walters

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 27, 2019
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 208215/S-12
Product Name and Strength:	Descovy (emtricitabine and tenofovir alafenamide) Tablets, 200 mg/25 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Gilead Sciences, Inc (Gilead)
FDA Received Date:	April 5, 2019 and August 26, 2019
OSE RCM #:	2019-830
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 REASON FOR REVIEW

Gilead submitted a prior approval efficacy supplement for Descovy (emtricitabine and tenofovir alafenamide) tablets in order to support the use of Descovy for pre-exposure prophylaxis of HIV-1 infection (PrEP). Subsequently, the Division of Antiviral Products requested that we review the proposed labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters*	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Our evaluation of the proposed Prescribing Information and Medication Guide did not identify areas of vulnerability that may lead to medication errors. Table 2 below includes identified issues with the currently marketed container label, DMEPA's rationale for concern, and the proposed recommendation to improve the container label.

Table 2: Identified Issues and Recommendations for Gilead Sciences, Inc. (entire table to be conveyed to Applicant)

Container Label			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	A Medication Guide is proposed to replace the currently marketed Patient Information	Per 21 CFR 208.24(d), the label of each container of drug product for which a Medication Guide is	Revise the Descovy container label to comply with 21 CFR 208.24(d).

	insert. We note a revised container label has not been submitted instructing authorized dispensers to dispense the Medication Guide to each patient.	required shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.	
General Container Label Recommendation			
1.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. See draft guidance https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf		

4 CONCLUSION

Our evaluation of the current in-use container label identified two areas for improvement. Above, we have provided our recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to the Applicant so that the recommendations are implemented prior to approval of this supplement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Descovy received on August 26, 2019 from Gilead Sciences, Inc.

Table 3. Relevant Product Information for Descovy	
Initial Approval Date	April 4, 2016
Active Ingredient	emtricitabine and tenofovir alafenamide
Indication	Treatment of HIV-1 infection • In combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg. • In combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35kg. HIV-1 Pre-Exposure Prophylaxis (PrEP) • For pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding receptive vaginal sex, in at-risk adults and adolescents weighing at least 35 kg. Individuals must have a negative HIV-1 test immediately prior to initiating Descovy for HIV-1 PrEP. (proposed)
Route of Administration	Oral
Dosage Form	Tablets
Strength	200 mg/25 mg
Dose and Frequency	Recommended Dosage for Treatment of HIV-1 Infection in Adults and Pediatric Patients Weighing at Least 25kg: • One tablet once daily with or without food Recommended Dosage for HIV-1 PrEP in Adults and Adolescents Weighing at Least 35 kg: • One tablet once daily with or without food
How Supplied	Bottles containing 30 tablets
Storage	(b) (4) [redacted] Keep container tightly closed. Dispense only in original container.
Container Closure	Bottle with child-resistant closure

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 24, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 208215 and Descovy. Our search identified two previous reviews[a,b], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Calderon, M. Review of Revised Label and Labeling for Descovy (NDA 208215). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 25. RCM No.: 2015-819-1.

[b] Calderon, M. Label and Labeling Review for Descovy (NDA 208215). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 DEC 08. RCM No.: 2015-819.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Descovy labels and labeling submitted by Gilead Sciences, Inc.

- Current In-Use Container Label
- Prescribing Information and Medication Guide received on April 5, 2019, available at: \\cdsesub1\evsprod\nda208215\0098\m1\us\114-labeling\draft\annotated\annotated-draft-labeling-text.pdf

G.2 Label and Labeling Images

- Current In-Use Container Label

(b) (4)

[redacted]

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: Aug 21, 2019

TO: Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Office of New Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

Himanshu Gupta, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Amendment of EIR review issued on 7/23/19 regarding surveillance inspection of (b) (4) (b) (4)

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) and ORA inspected the analytical portion of Study A15-137 conducted at (b) (4) for NDA 208215 S12 and (b) (4).

We did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The inspection classification is No Action Indicated (NAI). However, we discussed several items with the site management. We received the site's written responses to discussion items on 8/2/19. The purpose of this amended review is to update the review with the site's written responses and our recommendation on data for TFV in plasma.

1.1. Recommendation

Based on our review of the inspectional findings, we have the following conclusion and recommendation for the analytical data for study A15-137:

1) The data for tenofovir alafenamide (TAF) and emtricitabine (FTC) in plasma samples are reliable to support a regulatory decision.
2) The data for tenofovir (TFV) in plasma samples are reliable to support a regulatory decision.
3) The data from tissue, peripheral blood mononuclear cells (PBMC), cervicovaginal fluid (CVF), and rectal fluid (RF) samples are acceptable as supportive data, but not pivotal data supporting a regulatory decision.

2. Inspected Study

Study A15-137 (NDA 208215 S12 & (b) (4) [redacted])

"Exploratory Pharmacokinetic and Pharmacodynamic Study of Oral F/TAF for the Prevention of HIV Acquisition"

Analysis Period for Tissue, PBMCs, Plasma, CVF and RF Samples: May 2017 – May 2018

3. Scope of Inspection

ORA investigator Vanessa E. Coulter and OSIS scientists Xiaohan Cai, Ph.D. and Himanshu Gupta, Ph.D., audited the analytical portion of the above study at (b) (4) [redacted] from (b) (4) [redacted]

The inspection included a thorough examination of study records, facility, laboratory equipment, method validation, and sample analysis, and interviews with the site's management and staff.

4. Inspectional Findings

Bioanalysis of Tissue Samples:

We reviewed study records for determination of TFV, tenofovir diphosphate (TFV-dp), FTC, and emtricitabine triphosphate (FTC-tp) in tissue samples collected for study A15-137. We did not review the records for determination of TAF, dATP, and dCTP in tissue samples. Although the site validated the assay of TFV, TFV-dp, FTC, and FTC-tp in tissue homogenate, the tissue assay has limitations including:

1) Determinization on the recovery of TFV, TFV-dp, FTC, and FTC-tp from tissue was not feasible during the homogenization.
2) Long term and short-term storage stability for TFV, TFV-dp, FTC, and FTC-tp in tissue were not available.

For TFV-dp concentration (fmol/g) data from rectal tissue samples, the variability (CV%) among different tissue samples collected from the same subject at the same time point ranged from 7-111%. For example, the %CV of TFV-dp concentrations from four rectal tissue samples at 4 hours for subject (b) (6) is 105%. We confirmed that the site used the same procedure to homogenize all tissue samples. Although all samples were collected for a subject at the same time, the reasons for differences in the analyte concentrations in a subject's tissue samples include possible different biopsy locations, sample density, or variation in the collection procedure. Therefore, these differences in multiple tissue samples biopsied for one subject might be an important factor contributing the data variation.

Based on inherent limitations and observed data variation in tissue analysis, we recommend accepting the analytical data for all analytes in tissue samples as supportive data, but not pivotal data supporting a regulatory decision.

Bioanalysis of Peripheral Blood Mononuclear Cells (PBMC) Samples:

Details on the bioanalysis of PBMC samples are described in section 4.1, discussion items 1 and 2.

Bioanalysis of Plasma Samples:

Details on the bioanalysis of plasma samples are described in section 4.1, discussion items 3 and 4.

Bioanalysis of Cervicovaginal (CVF) and Rectal Fluid (RF) Samples:

The site validated the assay for determination of TAF in MeroCel homogenate. The site qualified the assay for determination of TFV and FTC in MeroCel homogenate. Based on the site's definition, the method qualification only requires one accuracy

and precision run before sample analysis. We observed several limitations for the analysis of CVF and RF:

1) The site could not obtain blank matrix of CVF and RF, thus has no data demonstrating parallelism between the CVF/RF and saliva, which was used as a surrogate matrix.
2) CVF and RF samples were collected using MeroCels sponge; however, the recovery of TAF, TFV, and FTC from Merocel sponge during the extraction process is unknown.
3) Stability data for TAF, TFV, and FTC in CVF or RF are not available.

Therefore, we recommend accepting the analytical data for all analytes in CVF and RF as supportive data, but not pivotal data supporting a regulatory decision.

At the conclusion of the inspection, we did not observe objectionable conditions. We did not issue Form FDA 483 to (b) (4) [redacted] However, we discussed the following items with management during the inspection and at close-out.

4.1. Discussion items

We discussed following items with the firm's management. We received the site's written response to discussion items on August 02 2019.

(b) (4) [redacted]

Site's Response: The site acknowledged that there were typographical errors on the accuracy acceptance criteria in the report. The site amended the report to correct the errors in reporting (**Attachment 1**). The site could conduct only one analysis per PBMC sample and they did not have any remaining sample left for sample reanalysis when a run failed. The site chose this less stringent criterion for run acceptance (<±20.0% bias, ±25.0% at the LLOQ) to avoid run failures and non-reportable data resulting from failed runs.

OSIS Evaluation: The site amended the report to correct the errors on acceptance criteria. The site chose less stringent criteria to avoid run failure because the limited sample volume would not allow for repeated analysis. When using the PBMC data as supportive information, the criteria used by the firm are acceptable.

(b) (4) [redacted]

Site's Response: The site acknowledged that they prepared calibrators and QC samples in the solution of methanol:water (70:30), instead of the same matrix as in subject samples. Because dATP and dCTP are present endogenously in blank PBMC samples, the site stated that it was not feasible to prepare the Low QCs in PBMC for dATP and dCTP, which were simultaneously analyzed with TFV-dp and FTC-tp in this assay. The site conducted experiments during method validation to show that there was minimal impact from PBMC. The site also evaluated middle QCs prepared using six lots of PBMC in one run and the results met the site's acceptance criteria. For future studies, the site updated their SOP (b) (4) [redacted] SOP-0342 to include matrix-matched QCs when appropriate.

OSIS Evaluation:
Although the site demonstrated minimal matrix effect in one run during method validation, the site did not monitor the performance of analytical runs during sample analysis for TFV-dp and FTC-tp using QCs prepared in PBMC lysate. We also observed that the long-term stability data for TFV-dp, FTC-tp, dATP, and dCTP in PBMCs were not available.

Therefore, we recommend accepting the data from the PBMC samples as supportive data, but not pivotal data supporting a regulatory decision. The site's corrective action is acceptable for future studies.

(b) (4) [redacted]

Site's Response: The site acknowledged that they did not have a standard practice to record sample movements time to calculate the duration of benchtop exposure of samples. The site implemented new procedures to track the time when the samples are removed from and returned to the freezers.

OSIS Evaluation: Without the records on sample movements in and out of freezers, we cannot reconstruct how long samples remained on the benchtop at room temperature. For the tissue, PBMC, CVF, and RF sample analysis, almost all samples were analyzed once without repeat, thus this finding has minimal impact on the tissue, PBMC, CVF, and RF data.

For plasma samples, the site established room temperature benchtop stability of 21 hours for TAF and 24 hours for TFV and FTC, and three freeze/thaw (F/T) cycles' stability for TAF, TFV, and FTC. We observed that most of the plasma samples went through 2 F/T cycles, with an exception of approximately 3% of samples subject to 3 F/T cycles. However, given the 21–24 hours stability data and F/T cycles information, it is plausible that all samples, including those with three F/T, did not exceed the established stability. Therefore, despite lack of documentation, this finding should have minimal impact to the reliability of TAF, TFV, and FTC data in plasma. The site's corrective action is acceptable for future studies.

(b) (4) [redacted]

Site's Response: The site acknowledged this finding. After the inspection, the site performed additional experiments to evaluate the potential conversion from TAF to TFV during short term benchtop and long-term frozen storage. Specifically, the firm compared the TFV concentration among freshly prepared TAF QC5 (400 ng/mL), TAF QC5 stored at room temperature for 24 hours, TAF QC5 and TAF QC4 (40 ng/mL) stored at -80 °C for 595 days. The results showed no conversion from TAF to TFV after room temperature storage for 24 hour and long-term frozen storage of 595 days. The site amended the validation report to include the results and conclusion (**Attachment 2**).

OSIS Evaluation: The site's evaluation on ex vivo conversion from TAF to TFV is acceptable. The results from the newly conducted experiments showed no increase of TFV concentration when storing TAF QC 400 ng/mL in plasma for 24 hours at room temperature and -80 °C for 595 days. Therefore, this item does not impact the data reliability of TFV in plasma.

4.2 Specific concerns from OCP

(b) (4) [redacted]

OSIS Evaluation: We verified that the TFV-dp concentrations were correctly reported in tissue samples. We noted that TFV-dp concentrations in almost all vaginal and cervical tissue samples were around the LLOQ level. TFV-dp data from the tissue samples suggest that the assay may not have adequate sensitivity to support the analysis of TFV-dp in vaginal and cervical tissue samples.

5. Conclusion

After review of the inspectional findings, we conclude the following recommendation for analytical data from study A15-137:

1) The data for TAF and FTC in plasma samples are reliable to support a regulatory decision.
2) The data for TFV in plasma samples are reliable to support a regulatory decision.
3) The data from tissue, PBMC, CVF, and RF samples are acceptable as supportive data, but not pivotal data to support a regulatory decision.

Final Classification:

NAI - (b) (4) [redacted]

cc: OTS/OSIS/Kassim/Kadavil/Mitchell/Fenty-Stewart

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Cai/Gupta
ORA/OMPTO/OBIMO/ORABIMOE.Correspondence@fda.hhs.gov

Draft: HG 8/7/19; XHC 8/8/19
Edit: YMC 8/8/19; JC 8/19/19

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/(b) (4)

OSIS File #: BE 8502

FACTS: (b) (4)

Attachments
Attachment 1: Amended bioanalytical report SAR-0623 for the determination of Tenofovir Diphosphate, Emtricitabine Triphosphate, dATP, and dCTP in Cells by LC-MS/MS
Attachment 2: Amended validation report for the determination of tenofovir alafenamide in human plasma using LC-MS/MS

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SEONGEUN CHO
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 23, 2019

TO: Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Office of New Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

Himanshu Gupta, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Surveillance inspection of (b) (4) [redacted]

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) and ORA inspected the analytical portion of Study A15-137 conducted at (b) (4) [redacted] for NDA 208215 S12 and (b) (4) [redacted].

We did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The inspection classification is No Action Indicated (NAI). However, we discussed several items with the site management. A review amendment may be submitted if the site submits written responses on discussion items.

1.1. Recommendation

Based on our review of the inspectional findings, we have the following conclusion and recommendation for the analytical data for study A15-137:

1) The data for tenofovir alafenamide (TAF) and emtricitabine (FTC) in plasma samples are reliable to support a regulatory decision.
2) The reliability of data for tenofovir (TFV) in plasma samples depends on the site's evaluation on the possible conversion from TAF to TFV in plasma samples during storage.
3) The data from tissue, peripheral blood mononuclear cells (PBMC), cervicovaginal fluid (CVF), and rectal fluid (RF) samples are acceptable as supportive data, but not pivotal data supporting a regulatory decision.

2. Inspected Study

Study A15-137 (NDA 208215 S12 & (b) (4) [redacted])

"Exploratory Pharmacokinetic and Pharmacodynamic Study of Oral F/TAF for the Prevention of HIV Acquisition"

Analysis Period for Tissue, PBMCs, Plasma, CVF and RF Samples: May 2017 – May 2018

3. Scope of Inspection

ORA investigator Vanessa E. Coulter and OSIS scientists Xiaohan Cai, Ph.D. and Himanshu Gupta, Ph.D., audited the analytical portion of the above study at (b) (4) [redacted] from 07/08/2019 to 07/12/2019.

The inspection included a thorough examination of study records, facility, laboratory equipment, method validation, and sample analysis, and interviews with the site's management and staff.

4. Inspectional Findings

Bioanalysis of Tissue Samples:

We reviewed study records for determination of TFV, tenofovir diphosphate (TFV-dp), FTC, and emtricitabine triphosphate (FTC-tp) in tissue samples collected for study A15-137. We did not review the records for determination of TAF, dATP, and dCTP in tissue samples. Although the site validated the assay of TFV, TFV-dp, FTC, and FTC-tp in tissue homogenate, the tissue assay has limitations including:

1) Determinization on the recovery of TFV, TFV-dp, FTC, and FTC-tp from tissue was not feasible during the homogenization.
2) Long term and short-term storage stability for TFV, TFV-dp, FTC, and FTC-tp in tissue were not available.

For TFV-dp concentration (fmol/g) data from rectal tissue samples, the variability (CV%) among different tissue samples collected from the same subject at the same time point ranged from 7-111%. For example, the %CV of TFV-dp concentrations from four rectal tissue samples at 4 hours for subject 310 is 105%. We confirmed that the site used the same procedure to homogenize all tissue samples. Although all samples were collected for a subject at the same time, the reasons for differences in the analyte concentrations in a subject's tissue samples include possible different biopsy locations, sample density, or variation in the collection procedure. Therefore, these differences in multiple tissue samples biopsied for one subject might be an important factor contributing the data variation.

Based on inherent limitations and observed data variation in tissue analysis, we recommend accepting the analytical data for all analytes in tissue samples as supportive data, but not pivotal data supporting a regulatory decision.

Bioanalysis of Peripheral Blood Mononuclear Cells (PBMC) Samples:

Details on the bioanalysis of PBMC samples are described in section 4.1, discussion items 1 and 2.

Bioanalysis of Plasma Samples:

Details on the bioanalysis of plasma samples are described in section 4.1, discussion items 3 and 4.

Bioanalysis of Cervicovaginal (CVF) and Rectal Fluid (RF) Samples:

The site validated the assay for determination of TAF in MeroCel homogenate. The site qualified the assay for determination of TFV and FTC in MeroCel homogenate. Based on the site's definition, the method qualification only requires one accuracy and precision run before sample analysis. We observed several limitations for the analysis of CVF and RF:

1) The site could not obtain blank matrix of CVF and RF, thus has no data demonstrating parallelism between the CVF/RF and saliva, which was used as a surrogate matrix.
2) CVF and RF samples were collected using MeroCels sponge; however, the recovery of TAF, TFV, and FTC from Merocel sponge during the extraction process is unknown.
3) Stability data for TAF, TFV, and FTC in CVF or RF are not available.

Therefore, we recommend accepting the analytical data for all analytes in CVF and RF as supportive data, but not pivotal data supporting a regulatory decision.

At the conclusion of the inspection, we did not observe objectionable conditions. We did not issue Form FDA 483 to (b) (4) [redacted]. However, we discussed the following items with management during the inspection and at close-out.

4.1. Discussion items

We discussed following items with the firm's management.

(b) (4) [redacted]

Site's Response: The site's written response to this discussion item is currently pending. During the inspection, the site acknowledged that there were typographical errors on the accuracy acceptance criteria in the report. The site could conduct only one analysis per PBMC sample and they did not have any remaining sample left for sample reanalysis when a run failed. The site chose this less stringent criterion for run acceptance (<±20.0% bias, ±25.0% at the LLOQ) to avoid run failures and non-reportable data resulting from failed runs.

OSIS Evaluation: The site may submit the amended report to correct the errors on acceptance criteria through the sponsor. The site chose less stringent criteria to avoid run failure because the limited sample volume would not allow for repeated

analysis. When using the PBMC data as supportive information, the criteria used by the firm are acceptable.

(b) (4) [redacted]

Site's Response: The site's written response to this discussion item is currently pending. The site acknowledged that they prepared calibrators and QC samples in the solution of methanol:water (70:30), instead of the same matrix as in subject samples. Because dATP and dCTP are present endogenously in blank PBMC samples, the site stated that it was not feasible to prepare the Low QCs in PBMC for dATP and dCTP, which were simultaneously analyzed with TFV-dp and FTC-tp in this assay. The site conducted experiments during method validation to show that there was minimal impact from PBMC. The site also evaluated middle QCs prepared using six lots of PBMC in one run and the results met the site's acceptance criteria.

OSIS Evaluation:
Although the site demonstrated minimal matrix effect in one run during method validation, the site did not monitor the performance of analytical runs during sample analysis for TFV-dp and FTC-tp using QCs prepared in PBMC lysate. We also observed that the long-term stability data for TFV-dp, FTC-tp, dATP, and dCTP in PBMCs were not available.

Therefore, we recommend accepting the data from the PBMC samples as supportive data, but not pivotal data supporting a regulatory decision.

(b) (4) [redacted]

Site's Response: The site's written response to this discussion item is currently pending. During the inspection, the site acknowledged that they did not have a standard practice to record sample movements time to calculate the duration of benchtop exposure of samples.

OSIS Evaluation: Without the records on sample movements in and out of freezers, we cannot reconstruct how long samples remained

on the benchtop at room temperature. For the tissue, PBMC, CVF, and RF sample analysis, almost all samples were analyzed once without repeat, thus this finding has minimal impact on the tissue, PBMC, CVF, and RF data.

For plasma samples, the site established room temperature benchtop stability of 21 hours for TAF and 24 hours for TFV and FTC, and three freeze/thaw (F/T) cycles' stability for TAF, TFV, and FTC. We observed that most of the plasma samples went through 2 F/T cycles, with an exception of approximately 3% of samples subject to 3 F/T cycles. However, given the 21-24 hours stability data and F/T cycles information, it is plausible that all samples, including those with three F/T, did not exceed the established stability. Therefore, despite lack of documentation, this finding should have minimal impact to the reliability of TAF, TFV, and FTC data in plasma.

(b) (4)

Site's Response: The site's written response to this discussion item is currently pending. During the inspection, the site acknowledged this finding.

OSIS Evaluation: The potential ex vivo conversion from TAF to TFV after sample collection might impact the TFV data in plasma. During sample storage, it was reported that TFV concentration increased due to conversion from TAF to TFV in untreated human plasma samples (Lizhi Zhao et al. 2019).

We do not have concern on the TAF data in plasma. During method validation, short and long-term stability QCs of TAF in plasma were within 85-115% of their nominal concentrations. Because the established TAF stability data covered all study samples after collection, the possible conversion has minimal impact on TAF data. In contrast, when TAF concentrations are significantly higher than TFV, even a small percentage of conversion, although within 15%, from TAF to TFV during sample storage might increase the TFV concentration. The percentage of concentration increase for TFV might be significant considering the relatively low concentration of TFV.

 (b) (4) [redacted]

As a result, it is important to evaluate whether the possible conversion from TAF to TFV impacts the TFV concentration using the current TFV assay. The reliability determination of TFV concentration data in plasma samples is pending on the site's further assessment and written response.

4.2 Specific concerns from OCP

(b) (4) [redacted]

OSIS Evaluation: We verified that the TFV-dp concentrations were correctly reported in tissue samples. We noted that TFV-dp concentrations in almost all vaginal and cervical tissue samples were around the LLOQ level. TFV-dp data from the tissue samples suggest that the assay may not have adequate sensitivity to support the analysis of TFV-dp in vaginal and cervical tissue samples.

5. Conclusion

After review of the inspectional findings, we conclude the following recommendation for analytical data from study A15-137:

1) The data for TAF and FTC in plasma samples are reliable to support a regulatory decision.
2) The reliability of data for TFV in plasma samples depends on the site's evaluation on the possible conversion from TAF to TFV in plasma samples during storage.
3) The data from tissue, PBMC, CVF, and RF samples are acceptable as supportive data, but not pivotal data to support a regulatory decision.

Final Classification:

NAI – (b) (4) [redacted]

cc: OTS/OSIS/Kassim/Choe/Kadavil/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Cai/Gupta
ORA/OMPTO/OBIMO/ORABIMOE.Correspondence@fda.hhs.gov

Draft: XHC 7/15/19, 7/17/19, 7/18/19; 7/19/19; 7/22/19; 7/23/19
HG 7/15/19, 7/16/19, 7/18/19
Edit: SA 7/19/2019, 7/22/2019; JC 7/22/2019, 7/23/19

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/(b) (4)

OSIS File #: BE 8502

FACTS: (b) (4)

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/s/

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HIMANSHU GUPTA
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STANLEY AU
07/23/2019 05:21:12 PM
Team Lead

SEONGEUN CHO
07/23/2019 09:38:52 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 14, 2019

TO: Debra Birnkrant, M.D.
Director
Division of Antiviral Products (DAVP)
Office of Antimicrobial Products (OAP)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE, OSIS

SUBJECT: Routine inspection of Eastern Virginia Medical School (EVMS), Norfolk, VA

Inspection Summary

Per the request of OND/OAP/DAVP, the Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of **Study A15-137 ((b) (4), cross-referenced in NDA 208215/S012)** conducted at Eastern Virginia Medical School (EVMS), Norfolk, VA.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

Recommendation

After reviewing the inspectional findings, I conclude the clinical data from the audited study are reliable to support a regulatory decision.

Inspected Study

(b) (4) (cross-referenced in NDA 208215/S012)

Study Number: A15-137

Study Title: "Exploratory Pharmacokinetic and Pharmacodynamic Study of Oral F/TAF for the Prevention of HIV Acquisition"

Dates of conduct: October 2016 – November 2017

Clinical Site: Eastern Virginia Medical School (EVMS) (Site ID #001)
Clinical Research Center (CRC)
601 Colley Avenue
Norfolk, VA 23507

ORA Investigator Melanie N. Daniels (OBIMO) inspected Eastern Virginia Medical School (EVMS), Norfolk, VA from May 20 – 23, 2019.

This was the first inspection of the clinical site. The inspection included a thorough examination of study records, subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events (AE), and case report forms (CRF).

Inspectional Findings

At the conclusion of the inspection, Investigator Daniels did not observe any objectionable conditions and did not issue Form FDA 483 to the site.

Conclusion

After reviewing the inspectional findings, I conclude that the clinical data from **Study A15-137** (b) (4) **, cross-referenced in NDA 208215/S012)** conducted at Eastern Virginia Medical School (EVMS), Norfolk, VA are reliable to support a regulatory decision.

Based on the inspectional findings, clinical data from studies of similar design conducted at Eastern Virginia Medical School (EVMS) between the end of audited **Study A15-137** (November 2017) and the end of the current surveillance interval should be considered reliable without an inspection.

Yiyue Zhang, Ph.D.
Staff Fellow

Final Classification

Clinical Site

NAI - Eastern Virginia Medical School (EVMS), Norfolk, VA
FEI#: 3008659573

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Zhang
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
ORA/OMPTO/OBIMO/DBIMOI/Daniels

Draft: YZ 06/13/2019
Edit: RCA 6/14/2019; AD 6/14/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Eastern Virginia Medical School (EVMS), Norfolk, VA

OSIS File#: BE 8502
FACTS: 11926277

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/s/

YIYUE ZHANG
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ARINDAM DASGUPTA
06/14/2019 12:17:22 PM