FDA Briefing Document

Meeting of the Antimicrobial Drugs Advisory Committee

August 7, 2019

Agenda: The committee will discuss supplemental new drug application (sNDA) 208215, supplement 12, DESCOVY (emtricitabine 200 mg and tenofovir alafenamide 25 mg) tablets, submitted by Gilead Sciences, Inc., proposed for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually-acquired HIV-1 infection among individuals who are HIV-negative and at risk for HIV.

Food and Drug Administration
Center for Drug Evaluation and Research
DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought data to support the oral fixed-dose combination of emtricitabine 200 mg and tenofovir alafenamide 25 mg (Descovy®) for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually-acquired HIV-1 infection in at-risk adults and adolescents to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1. INTRODUCTION AND CHARGE TO THE COMMITTEE

On July 16, 2012, the FDA approved the fixed-dose combination of emtricitabine (FTC) 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg (Truvada®, F/TDF) for pre-exposure prophylaxis (PrEP) 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 iPrEx trial (NCT00458393) in men and transgender women who have sex with men (MSM/TGW) {Grant et. al. 2010} and 2) the Partners PrEP trial (NCT00557245) in heterosexual HIV discordant 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) by a modified intent-to-treat analysis. In both trials, and numerous studies since, PrEP efficacy was highly correlated with the degree of 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. Headache, nausea, abdominal pain and weight loss were the main clinical safety findings associated with use of F/TDF for PrEP, 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 laboratory 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 safety and adherence data from the dedicated open-label study ATN 113 (NCT01769456) in young MSM 15 to 17 years of age and extrapolation of adult efficacy data {Hosek et al. 2017}. Truvada remains the only drug product approved for a PrEP indication.

Despite demonstrated safety and efficacy, awareness and uptake of Truvada for PrEP in the U.S. were very limited following the approval. However, the Centers for Disease Control and Prevention (CDC) estimates that between 2014 and 2016, the annual number of PrEP users aged ≥ 16 years increased by 470%, from 13,748 to 78,360 in the U.S. {Huang et al. 2018}, and that current PrEP awareness and uptake are up to 90% and 35%, respectively, among high-risk MSM {Finlayson et al. 2019}. Other sources estimate the number of current PrEP users in the U.S. to be over 250,000 {AVAC 2019}.

Increases in PrEP uptake have mostly been in select populations, namely white, urban, educated MSM. Overall uptake of PrEP in the U.S., however, remains low. The CDC estimates that 1.1 million people in the U.S. have indications for PrEP {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 populations disproportionally affected by the current 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 nation's ongoing opioid crisis {Rudd et al. 2016}. To illustrate, the CDC notes that among the 1.1 million U.S. adults with indications for PrEP, 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, respectively {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 estimated 40,000 new HIV diagnoses reported in the U.S. each year, an incidence rate that has remained constant since 2012 {CDC 2017}, point to gaps in the nation's PrEP implementation efforts. In response, the U.S. government announced an ambitious new initiative in February 2019 to reduce new HIV 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 daily usage and frequent provider visits {John et al. 2017}. With regards to the latter, new regimens and delivery methods to improve acceptability, adherence and effectiveness of PrEP are needed and are 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 this supplemental New Drug Application (NDA 208215/S-012), Gilead Sciences, Inc. (Applicant) is seeking a PrEP indication for another once daily tablet, the oral fixed-dose combination of emtricitabine 200 mg and tenofovir alafenamide 25 mg (Descovy®, F/TAF). The proposed PrEP indication is for use in at-risk adults and adolescents weighing at least 35 kg, mirroring the current indication for F/TDF. The Applicant's rationale for proposing Descovy as PrEP rests primarily on its approval for the treatment of HIV-1 infection, its potential safety advantages over F/TDF (demonstrated chiefly by improved biomarker test results), and efficacy results from 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 clinical data to support the use of Descovy for PrEP are derived from the primary analysis of the DISCOVER trial. Results from two external (non-Gilead) IND Phase 1 clinical pharmacokinetic (PK) studies are provided to support the extrapolation of PrEP efficacy to cisgender women. The Applicant submitted published results from a single-dose PK study of TAF {Cottrell et al. 2017} and a clinical study report and datasets from a multiple-dose PK study of F/TAF and F/TDF {Schwartz et al. 2018} for FDA review.

Upon review of the clinical data from the DISCOVER trial, the FDA has concluded that the data support the proposed PrEP indication for Descovy in MSM/TGW at risk of HIV infection. With respect to the proposed indication in cisgender women, based on a review of the available literature, the FDA considers that local tissue drug concentrations at the site of potential HIV exposure are important to the prevention of HIV transmission. In the absence of clinical efficacy data with Descovy in cisgender women, evidence of adequate drug concentrations in cervicovaginal tissues with F/TAF dosing is considered necessary to allow for extrapolation of Truvada efficacy in support of a female Descovy PrEP indication. After review of the submitted data to support such an extrapolation approach, the FDA is uncertain that the data can support the efficacy of Descovy as PrEP in cisgender women.

This Advisory Committee Background Document provides a summary of the available literature and the data submitted in support of this application. We provide a discussion of the potential contribution of mucosal tissue drug concentrations to PrEP efficacy and discuss the data provided to support an extrapolation of efficacy to cisgender women. The charge to the advisory committee is to determine whether the data from the DISCOVER trial support the use of Descovy for PrEP in men and TGW who have sex with men and are at risk of HIV infection, and whether the available data support extrapolation of Truvada PrEP efficacy to the use of Descovy as PrEP in cisgender women at risk of HIV infection. If the data are not deemed adequate to support an indication in any of the proposed populations, the FDA asks the advisory committee to provide input as to what additional studies or trials may be needed, and what clinical trial designs would be adequate to support an indication in specific sub-populations (e.g. MSM, TGW or cisgender women).

2. BACKGROUND

a. Descovy® (emtricitabine/tenofovir alafenamide)

As both Truvada and Descovy contain 200 mg FTC, and plasma concentrations of FTC are comparable following administration of each drug, this discussion will focus on the role of TAF in the safety and efficacy of Descovy for HIV-1 PrEP. 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. Several considerations, however, support the inclusion of FTC as part of PrEP: 1) PK studies suggest that the active metabolite of FTC, emtricitabine-triphosphate (FTC-TP), accumulates quickly in mucosal tissues, with better concentrations in vaginal tissue and cells compared to tenofovir diphosphate (TFV-DP) {Patterson et al. 2011}, 2) animal studies in macaques suggest better protection against simian/human immunodeficiency virus (SHIV) infection with the combination of FTC and tenofovir over tenofovir monotherapy in rectal and vaginal challenge models {Subbarao et al. 2006; Garcia-Lerma et al. 2008; Garcia-Lerma et a. 2008; Garcia-Lerma et al. 2011; Massud et al. 2019}, and 3) the combination of two nucleoside reverse transcriptase inhibitors (NRTIs) is expected to increase the barrier to resistance.

Like TDF, tenofovir alafenamide is a prodrug of tenofovir (TFV) currently approved for the treatment of HIV-1 and hepatitis B virus (HBV). While the intracellular active metabolite TFV-DP is the same for both drugs, TAF and TDF exhibit distinct PK properties. TDF is mostly hydrolyzed to TFV, the major circulating form in plasma, whereas TAF is not significantly hydrolyzed and circulates as TAF in plasma. Consequently, 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. This marked reduction in circulating TFV levels is believed to be responsible for the improved measures of bone and renal safety observed with TAF relative to TDF in treatment trials of HIV and chronic HBV infection. On the other hand, fasting plasma lipid levels tend to be higher with TAF administration compared to TDF because systemic exposures of TFV are higher with TDF and TFV appears to have lipid-lowering effects {Cid-Silva et al. 2019}.

Cross-study comparison of two single-dose studies suggest that PK differences between TAF and TDF also extend to differences in observable TFV-DP concentrations in mucosal tissues relevant to HIV transmission. 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 administration of TAF 25 mg, and could not be quantified in any samples collected after 72 hours {Cottrell et al. 2017}. These findings contrasted with historical data from a similarly conducted single-dose PK study of TDF by the same investigators {Cottrell et al. 2016}. In comparing these data, TFV-DP exposures following a single 25 mg dose of TAF were reportedly more than 10-fold lower in rectal tissue compared with administration of TDF 300 mg. Furthermore, TFV-DP was unquantifiable in 35% more female genital tract tissue samples and 75% more rectal tissue samples with TAF compared to TDF dosing. Given that 91% of tissue samples were unquantifiable, results from this single-dose TAF study were inconclusive (and the authors concluded that additional PK studies exploring higher single or multiple doses were needed). Nonetheless, the results highlighted the limited understanding of TAF pharmacology at the mucosal tissue level and raised questions about the role of TAF in HIV prevention.

Similarly, CDC investigators working with a rectal challenge model of SHIV infection in rhesus macaques found that while TAF enhances the delivery of TFV-DP in PBMCs as compared to TDF, this relationship was not maintained in rectal tissues, where TFV-DP concentrations were about an order of magnitude lower than those achieved with TDF {Massud et al. 2016}. Nonetheless, these macaque studies were able to demonstrate significant protection from SHIV with F/TAF dosed 24 hours before and 2 hours after rectal challenge, comparable to that previously observed with F/TDF in the same macaque model. It should be noted, however, that there are potentially substantive differences between these models and the human experience, including differences in drug exposures and the use of surrogate viruses, and the predictive value of these models for efficacy in humans exposed to HIV-1 is unclear.

b. The Role of Mucosal Tissue Drug Exposure and HIV 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 mucosal tissues of the vagina and rectum play a critical role in HIV-1 acquisition, the relative importance of drug exposures 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}, one might speculate that local tissue exposures alone cannot provide complete protection. And yet, 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}, suggest that high local tissue drug concentrations, in the absence of significant systemic drug exposure, can independently reduce the risk of HIV infection from vaginal exposure. (In macaque studies, both oral F/TDF and tenofovir gel were found to be highly protective {Garcia-Lerma et al. 2010; Dobard et al. 2012; Garcia-Lerma et al. 2008; Parikh et al. 2009; Radzio et al. 2012}). It has been suggested that systemic drug concentrations may therefore 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}.

Seroconversion outcomes in clinical trials of oral PrEP in men and women may also provide insight into the role of mucosal tissue drug exposure in HIV transmission. 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 more recently {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 cisgender women, FEM-PrEP and VOICE {Van Damme et al. 2012; Marrazzo et al. 2015}, where less than 30% of subjects had drug exposure evidence of recent product use. However, similarly low rates of adherence among MSM/TGW in the iPrEx trial still resulted in a 42% risk reduction, suggesting preferential activity of F/TDF for prophylaxis of rectal HIV exposures {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 to vaginal tissue as measured in tissue homogenates {Patterson et al. 2011; Louissaint et al. 2014; Seifert et al. 2016}. However, results obtained from tissue cells (as opposed to homogenates) show mixed results, from no difference {Louissaint et al. 2014} to 13-fold higher {Seifert et al. 2016} concentrations in colorectal tissue cells as compared to cervicovaginal tissue cells. Presumably, such variability in drug concentrations between the female genital tract and rectal tissue would not be relevant if systemic drug exposure were the main determinant of PrEP efficacy, as the plasma and intracellular PK profiles of FTC and TDF are comparable between men and women. Taken together, though, these indirect observations suggest that drug exposures in various mucosal tissues may play an important role in the prevention of HIV infection. Accordingly, PrEP guidelines published by the CDC have included information about the time to achieve maximum concentrations of TFV-DP in various compartments (approximately 7 days for rectal tissue and 20 days for cervicovaginal tissues) {CDC 2018}, and some state guidelines have followed suit in their prescribing recommendations {New York State Department of Health 2017}.

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

In contrast, nonclinical studies in rhesus macaques, while also reporting differences in active drug concentrations between vaginal and rectal tissues and between TAF and TDF, have nonetheless shown significant protection with oral dosing of F/TDF and F/TAF against vaginal and rectal challenges with SHIV {Garcia-Lerma et al. 2010; Radzio et al. 2012; Massud et al. 2016; Massud et al. 2018}. These nonclinical observations raise questions about the contribution of tissue versus systemic drug concentrations to oral tenofovir-based PrEP efficacy. However, an earlier rectal challenge study in rhesus macaques using a high dose of TAF monotherapy dosed 3 days prior to rectal challenge (as opposed to before and after) failed to show a prophylactic effect despite high levels of TFV-DP in PBMCs {Garcia-Lerma et al, 2011}. Similar results were obtained in a vaginal challenge model with TAF

monotherapy, despite dosing before and after viral challenge and notably with comparable TFV-DP concentrations in PBMCs between infected and uninfected macaques {Massud et al. 2019}.

In conclusion, the FDA considers it is important to compare TFV-DP concentrations in the same mucosal tissues if bridging of efficacy between F/TDF and F/TAF is being proposed. Bridging of efficacy results from men to cisgender women based on mucosal tissue concentrations, however, is not possible because the effective drug concentrations could be different for rectal and vaginal HIV exposures.

c. Regulatory Background

Discussions with the FDA regarding a Descovy PrEP indication were initiated in 2016. The initially proposed pivotal trial design consisted of a single-arm, open-label, Phase 3 trial of F/TAF in high-risk MSM/TGW for 24 weeks using historical controls (i.e., the placebo HIV incident rates from Truvada PrEP trials in MSM). Integral to this proposal was the supposition that intracellular TFV-DP levels in PBMCs achieved with F/TAF could serve as a PK bridge to efficacy data from the Truvada PrEP trials. However, given reports of lower (i.e., unquantifiable) TFV-DP concentrations in rectal tissue with TAF dosing relative to TDF, and uncertainty about the relative importance of mucosal tissue versus systemic drug exposures 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 recommended instead an active-controlled, non-inferiority trial of 96 weeks duration with Truvada as the comparator to support licensure.

With respect to the ensuing Phase 3 trial GS-US-412-2055 (DISCOVER) in MSM/TGW, 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 prior PrEP trials of Truvada in MSM (i.e., iPrEx, PROUD, and IPERGAY).

While two adequate and well-controlled trials are generally recommended to provide substantial evidence of efficacy and safety for registration, the FDA considered that a single trial may be acceptable if adherence in the trial was high and the treatment effect was robust with strong internal consistency. (b) (4) .

Since the pre-IND phase, the FDA encouraged the Applicant to also consider conducting a trial of Descovy in cisgender women at high risk of HIV-1 acquisition. In subsequent discussions, the Applicant reported challenges in designing a PrEP trial in this population because of difficulties in identifying a suitable study design or a relevant female cohort for study in sub-Saharan Africa, where such a trial would be undertaken. The Applicant also expressed concerns that adherence and perception of risk were highly variable in 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. Subsequent communications made it clear the Applicant planned to pursue an extrapolation strategy to support a Descovy PrEP indication in cisgender

women. Of note, during this same time period, other Phase 3 prevention trials in women were either initiated or ongoing in sub-Saharan Africa (e.g., HPTN 084 for injectable cabotegravir versus daily oral Truvada [NCT03164564] and the ASPIRE and Ring Study trials of dapivirine vaginal ring versus placebo {Baeten et al. 2016; Nel et al. 2016}. However, these trials are evaluating superiority of non-oral regimens compared to daily oral regimens or placebo, and it is unlikely that superiority of F/TAF to F/TDF could be demonstrated since both are daily oral tablet formulations. Noninferiority trials using F/TDF as a control in cisgender women have not been possible due to the inability to define a noninferiority margin because previous preventive efficacy results of F/TDF in this population have been inconsistent.

(b) (4)

At a November 2018 meeting to discuss the content of the present efficacy supplement, the Applicant described its strategy to support a broad indication for Descovy PrEP in adults and adolescents. Safety and efficacy data from the pivotal DISCOVER trial would support an indication in MSM/TGW. An indication in cisgender women would be supported by 1) extrapolation of F/TAF efficacy from the DISCOVER trial via comparable systemic drug exposures, 2) extrapolation of F/TDF efficacy in cisgender women from the Partners PrEP trial via comparable or greater vaginal tissue drug concentrations, and 3) extrapolation of safety in HIV-infected men and women from the TAF development program; in addition, nonclinical vaginal challenge studies in pigtail macaques would provide supportive evidence. Finally, an adolescent indication would be supported by extrapolation of adult efficacy data and PK and safety data in HIV-infected adolescents treated with TAF-based regimens.

The current efficacy supplement was submitted on April 5, 2019. A priority review was granted because the Applicant used a Rare Pediatric Disease Priority Review Voucher for this application.

3. Data to Support a Descovy PrEP Indication

a. Men and Transgender Women Who Have Sex with Men

Interim trial data from the Phase 3 DISCOVER trial, with a cutoff date of January 31, 2019, were submitted to support a Descovy PrEP indication in MSM/TGW. The trial design and results are summarized herein.

DISCOVER Study Design

The DISCOVER trial is an ongoing multinational, Phase 3, randomized, double-blind trial to compare safety and efficacy of F/TAF versus F/TDF in HIV-1 negative adult men and TGW who have sex with men and are at high risk of HIV-1 infection. The trial is being conducted in 94 sites across 11 countries in

North America and Europe in cities known to be historic urban epicenters of the HIV epidemic and that have 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 trial planned to enroll 5000 subjects to receive blinded study drug for 96 weeks. The sample size was calculated based on the treatment effect observed in previous PrEP trials in MSM (i.e., iPrEx, PROUD, IPERGAY). A sample size of 2500 participants in each arm with 1:1 randomization was expected to provide at least 82% power to show noninferiority of F/TAF to F/TDF. The noninferiority margin of 1.62 and an HIV-1 infection rate of 1.44 per 100 person-years (PY) were based on results from prior PrEP trials in MSM.

Eligible participants were HIV-1 negative MSM or TGW aged ≥ 18 years who had at least one of the following: condomless anal intercourse with at least two 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. Each participant had to have a minimum estimated glomerular filtration rate according to the Cockcroft-Gault formula ($eGFR_{CG}$) of 60 mL/min and no history of osteoporosis or bone fragility fractures. Participants with suspected or known active, serious infection(s); evidence of acute viral hepatitis A, B, or C infection; or evidence of chronic hepatitis B virus (HBV) infection were excluded. Prior or current use of F/TDF PrEP was not an exclusion criterion.

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; safety assessments including monitoring of adverse events and concomitant medications, physical examinations, weight, vital signs measurements, and clinical laboratory tests (hematology, chemistry, urinalyses including markers of renal function); screening for sexually-transmitted infections (STIs), and hepatitis C and B virus; and collection of plasma samples to evaluate TFV and FTC plasma PK. A single pre-dose PBMC sample was collected at Week 4 to evaluate intracellular concentrations of TFV-DP and FTC-TP. Subjects also self-reported demographic characteristics, sexual risk behaviors, study drug adherence, and recreational drug and alcohol use at each visit via computer-assisted self-interview (CASI).

A substudy assessing hip and spine bone mineral density (BMD) changes at Weeks 48 and 96 by dual energy x-ray absorptiometry (DXA) tests was conducted in a subset of 400 subjects (200 per arm), providing at least 95% power to detect a 1.54% difference between groups.

Adherence to study drug was assessed by self-report and pill count. In addition, two substudies were conducted based on TFV-DP concentrations in red blood cells, an indicator of long-term adherence, from dried blood spot (DBS) samples:

1) a cohort substudy in approximately 10% of subjects randomly pre-selected to estimate overall rate of adherence, and

2) a case-control substudy 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.

The severity of adverse events and laboratory abnormalities were graded based on the Applicant's toxicity grading scale, provided in the protocol.

The primary endpoint is the incidence of HIV-1 infection per 100 PY, evaluated when all subjects had completed a minimum follow-up of 48 weeks and at least 50% had completed 96 weeks, or had prematurely discontinued from study. This endpoint was selected based on FDA guidance on the development of systemic drug products for PrEP {FDA 2018}. The primary analysis is evaluated in the Full Analysis Set (FAS), where the FAS includes all subjects who 1) are randomized into the study, 2) have received at least 1 dose of study drug, 3) are not HIV positive on Day 1 (defined as subjects with either negative Covance antibody test results at the first post baseline assessment or negative local lab Day 1 rapid tests), and 4) have at least one post-baseline HIV laboratory assessment (from either local or central laboratory).

Interim analyses were performed after 50% of participants reached Weeks 24, 48, and 72, respectively; an alpha of 0.00001 was spent for each interim analysis. Therefore, the significance level for the 2-sided test in the primary analysis was 0.04997 (corresponding to 95.003% CI). Noninferiority of F/TAF to F/TDF was to be concluded if the upper bound of the 2-sided 95.003% CI of the rate ratio in the HIV infection incidence rate was less than 1.62.

There are 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 beta-2-microglobulin to creatinine ratio
- percentage change from baseline in urine retinol binding protein (RBP) to creatinine ratio
- distribution of urine protein and urine protein to creatinine ratio (UPCR) categories
- change from baseline in serum creatinine

To control for the overall type I error rate for these multiple testings, multiplicity adjustments were performed with a fallback procedure and prespecified 2-sided alpha levels.

DISCOVER Results

As previously noted, the analysis of the primary endpoint was conducted when all subjects had completed 48 weeks of follow-up and half had completed 96 weeks of follow-up or had discontinued the trial. The data cutoff date for this submission was January 31, 2019.

Study Participants

Screening for the DISCOVER trial began in September 2016 and full enrollment was completed in May 2017. Of 5857 participants screened, 364 failed screening, of which 49 were HIV positive at screening.

A total of 5387 subjects were randomized and received study drug (F/TAF 2694, F/TDF 2693). Within this cohort, demographics and baseline characteristics were well balanced between the treatment groups. The vast majority (98.6%) of subjects were MSM; TGW made up only 1.4% of the study population. Median age was 34 years (range: 18-74 years); 12% of subjects were below the age of 25 years. Most subjects were white (83%); 8.8% were black/mixed black, 4% were Asian, and about 25% were Hispanic or Latino. The majority (59.8%) of subjects were in the U.S., of which 40% were in the U.S. South. In general, this was a well-educated cohort; the highest educational level attained by 57% of the study population was 4 years of college or higher. Seventy-one (71) percent of subjects were employed full-time. At baseline, mean (SE) $eGFR_{cg}$ was 127.2 (0.467) mL/min.

While the subject demographics skewed towards older, white, educated MSM (consistent with the majority of current PrEP users in the U.S.), this was still a sexually high-risk cohort. At screening, less than 40% reported routinely using condoms to manage HIV risk, and less than 30% asked their partners to use condoms. Of those subjects with screening CASI information (n=5199), 61% reported two or more unique unprotected receptive anal intercourse (URAI) partners in the 90 days prior to screening (mean [SE] 3.52 [0.084] partners) and 63% reported 2 or more unique unprotected insertive anal intercourse (UIAI) partners during that same time period (mean [SE] 4.18 [0.097] partners). For the 24 weeks prior to screening, 9.9% of subjects reported a history of rectal gonorrhea, 12.5% a history of rectal chlamydia, and 9.2% a history of syphilis. At screening, the proportion of subjects diagnosed with STIs, based on laboratory results, was as follows: gonorrhea rectal 4.4%, urethral 0.6%, pharyngeal 5.1%; chlamydia rectal 7.3%, urethral 2.2%, 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 post-exposure prophylaxis (PEP) in the 12 months prior to screening, and 23.1% reported any prior use of Truvada for PrEP. At baseline, 16.8% of subjects were taking PrEP prior to randomization. Finally, 43.8% of subjects were uncircumcised.

As of the data cutoff date, 85.8% of treated subjects were still in the study and 83.6% remained on study drug, with similar rates of drug discontinuation in both arms. Among the 882 (16.4%) subjects who prematurely discontinued study drug, the reasons for stopping were as follows: lost to follow-up (42.1%), subject decision (41.7%), adverse event (9.6%), noncompliance with study drug (2.3%), investigator's discretion (1.7%), HIV-1 infection (1.5%), protocol violation (0.8%), and death (0.3%). By Kaplan-Meier estimate, there was no difference between treatment groups in the time to premature study drug discontinuation.

Rates of discontinuation were higher among TGW participants. Among the 74 treated TGW subjects, 26 (35.1%) prematurely discontinued study drug (F/TAF 16, F/TDF 10) and 24 (32.4%) dropped out of the study as of the cutoff date (2 subjects stopped drug but remained on study). The reasons for prematurely stopping study drug were as follows: lost to follow-up (14 subjects [53.8%]), subject decision (8 subjects [30.7%]), adverse event (3 subjects [11.5%]), and noncompliance with study drug (1 subject [3.8%]).

Efficacy Results

Primary Efficacy

In the primary efficacy analysis, 22 (0.4%) of 5335 participants (FAS) were infected with HIV-1. Infections in each treatment group and the analysis results are provided below (Table 1).

Table 1: Primary Efficacy Analysis, FAS Population (DISCOVER)

		FTC/TAF (N=2670)	FTC/TDF (N=2665)	Ratio of F/TAF vs. F/TDF (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 Person-years		**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]

[a] Ulm (1990) method was used to calculate the exact 95% CI for individual rate (a single Poisson parameter)

[b] 95.003% was constructed using generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect

Source: FDA analysis of ADEFF dataset from DISCOVER trial

In the FAS population, the rate ratio for the HIV incidence rate (F/TAF vs. F/TDF) was 0.468 (95.003% CI: 0.191, 1.149). As the upper bound of the 2-sided confidence interval (CI) for the incidence rate ratio was less than the prespecified noninferiority margin of 1.62, noninferiority of F/TAF to F/TDF was demonstrated. While there were less HIV infections in the F/TAF group than in the F/TDF group, the current trial is not large enough to support superiority claims of F/TAF to F/TDF.

Adherence

By all measures, estimated adherence to study drugs was high in this trial. By CASI questionnaire, the median self-reported adherence was greater than 95% at all visits. Median pill-count adherence was 98% in both treatment arms. In the DBS 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, confirmed the high adherence results of the DBS substudy.

Risk Behaviors and STIs

Sexual risk behaviors in this study population did not significantly change from baseline. The percentage of subjects who reported condomless sex at each visit remained consistently high (approximately 90%) through Week 96, as did the reported numbers of URAI or UIAI partners. Likewise, the laboratory-based STI incidence rates remained persistently high throughout the trial, with about 57% of subjects diagnosed with at least one gonococcal or chlamydial infection post-baseline. Given these findings, and the high-risk behaviors reported at baseline and the percentage of subjects with STIs diagnosed at screening, there is no evidence to suggest risk compensation was occurring in the DISCOVER trial.

HIV Seroconverters

Based on blinded medical review of the data, of the 22 subjects who seroconverted during the DISCOVER trial, 5 subjects (F/TAF 1, F/TDF 4) were suspected to have a baseline HIV-1 infection. Most of these subjects were diagnosed within the first few weeks of the trial and each had a potential HIV exposure around the time of study entry. Four of these subjects had genotypic resistance to FTC. In a sensitivity analysis, exclusion of these 5 subjects did not change the primary conclusion of noninferiority of F/TAF to F/TDF.

All 22 seroconverters in the trial were MSM and none was a TGW. Median age was 27 years and 7 (32%) subjects were below the age of 25 years. Six (27%) subjects were young MSM of color (under 25 years of age and black/mixed black or Hispanic/Latino). Median time to HIV diagnosis was 231 days.

Compared to subjects not infected with HIV-1, the group of seroconverters 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. More importantly, results of the DBS case-control substudy suggest poor adherence to study drug within this group. Median TFV-DP levels on DBS at the HIV-1 diagnosis visit were significantly lower in the seroconverters compared with the uninfected matched control subjects. Of the 7 seroconverters in the F/TAF group, one subject with high TFV-DP levels was suspected to have baseline HIV-1 infection, five had low TFV-DP levels, and one had medium TFV-DP levels. Of the 15 seroconverters in the F/TDF group, four with high TFV-DP levels were suspected to have baseline HIV-1 infection, 10 had low levels of TFV-DP, and 1 with a missing DBS sample at the HIV diagnosis visit had high TVF-DP levels as imputed from a DBS sample collected 12 weeks prior.

Of note, 9 of the 22 seroconverters prematurely discontinued study drug or had drug interruption prior to seroconversion. The reasons for stopping drug were: subject decision (2 subjects per arm), adverse event (F/TAF 1 subject, F/TDF 2 subjects) and noncompliance (F/TDF 2 subjects).

Resistance

Viruses expressing M184I or M184V, which confer resistance to emtricitabine, were detected among 4 of the 19 subjects who seroconverted during the trial and were included in the resistance analysis. All four subjects harboring resistant viruses were seronegative at baseline and received F/TDF. It is unclear whether the resistant viruses were resistant when transmitted or selected during the first month of receiving PrEP. These results are consistent with those of previous Truvada PrEP trials (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 a resulting lack of selective pressure.

Summary of Efficacy

Efficacy data from the DISCOVER trial indicate that F/TAF and F/TDF are similar in reducing the risk of HIV-1 infection in at-risk MSM/TGW. Despite the low number of HIV infections observed in the trial, noninferiority of F/TAF to F/TDF was demonstrated.

Of note, the HIV infection rates observed in DISCOVER were lower than those observed in previous trials of oral PrEP in MSM, potentially raising concerns about whether the constancy assumption was maintained. In this case, similarity between F/TAF and F/TDF can mean either that both drugs were effective or neither drug was effective because the population was not at substantial risk. However, several factors suggest that the DISCOVER trial had adequate assay sensitivity to assess noninferiority. For one, the design of the trial was consistent with previous trials in MSM that demonstrated efficacy of F/TDF compared with placebo. Second, the enrolled study population was at considerable risk for HIV-1 infection based on their risk behaviors (as determined by self-reporting and laboratory-based STI rates during the trial) and the high HIV incidence rates in their communities (as determined by site selection and background HIV transmission rates among MSM not taking PrEP for the geographical areas where the U.S. study sites were located). Given these observations, the likeliest explanation for the low number of HIV infections observed in the DISCOVER trial is 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.

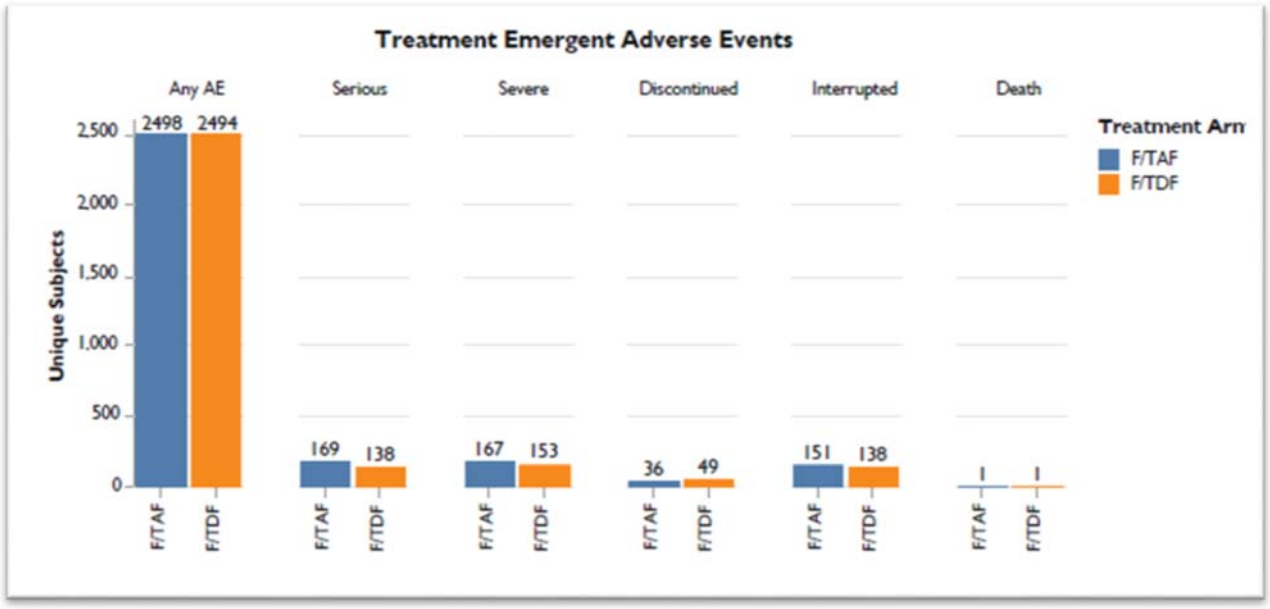
Resistance was not observed among seroconverters in the F/TAF group, and what resistance was found in the F/TDF group (n=4) was in subjects suspected of having a baseline HIV-1 infection. However, the numbers of HIV infections observed are too small to draw any conclusions regarding the relative risk of resistance.

Safety Results

As of the data cutoff date, the median (Q1, Q3) exposure to study drug was 85.7 (83.7, 96.7) weeks in the F/TAF arm and 86.7 (83.9, 96.6) weeks in the F/TDF arm.

Both F/TAF and F/TDF were safe and well tolerated in this trial population. The incidence rates of major clinical safety events were similar in both treatment groups (Figure 1). Furthermore, within these treatment-emergent adverse event (TEAE) categories, there were no notable differences between groups with respect to the types, frequency, timing or severity of TEAEs, most of which were mild or moderate in severity.

Figure 1: Summary of Adverse Events (DISCOVER)



Source: FDA analysis of ADAE dataset from DISCOVER trial

There were two treatment-emergent deaths, one in each group: 1) road traffic accident in the F/TAF group, and 2) death due to unknown causes on Study Day 20 in a 26-year-old man in the F/TDF group. Neither death was considered related to study drug by the investigators. An additional death due to metastatic squamous cell carcinoma occurred 54 days after the last dose of study drug in a 52-year-old man in the F/TDF group.

The most commonly reported TEAEs were STIs, with chlamydial and gonococcal infections reported in 41% and 43% of subjects, respectively. Infections aside, the next most common TEAEs were diarrhea (16%), nausea (7%), headache (7%), and fatigue (6%), with equal frequency rates in both groups.

Treatment-emergent AEs leading to study drug discontinuation occurred in less than 2% of subjects in either group. Gastrointestinal (GI) disorders (e.g., diarrhea, nausea, vomiting, abdominal pain or distension, and flatulence) were the most common AEs leading to permanent drug discontinuation in both groups (F/TAF 0.3%, F/TDF 0.6%).

Adverse drug reactions (i.e., TEAEs considered related to study drug by the investigators) were reported in 20% and 23% of subjects in the F/TAF and F/TDF groups, respectively. The most common drug reactions were diarrhea (F/TAF 5%, F/TDF 6%), nausea (F/TAF 4%, F/TDF 5%), fatigue (F/TAF 2%, F/TDF 3%), headache (2% each), and abdominal pain (F/TAF 2%, F/TDF 3%). (For the analysis of abdominal pain, FDA reviewers grouped the similar terms of abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, and abdominal discomfort.)

For the GI-related TEAEs of diarrhea, nausea, and abdominal pain, a distribution of events by time analysis indicates that most of these events occurred within the first 4 weeks of treatment, consistent

with the "start-up syndrome" previously described in PrEP clinical trials in MSM {Grant et al. 2010; Glidden at al. 2016}.

There were no differences within groups or between groups with respect to clinically relevant changes from baseline in chemistry or hematology laboratory parameters, vital signs, or weight. There were no Hy's law cases to suggest drug-induced liver injury with either F/TAF or F/TDF.

There are three main safety concerns to consider with comparing TAF to TDF: renal safety (particularly proximal renal tubulopathy [PRT]), bone mineral density changes, and changes in fasting lipid levels. The remainder of the DISCOVER safety analysis will focus on these issues.

Renal Safety

Small but significant differences were observed between the treatment groups at each visit with respect to the mean change from baseline in serum creatinine and $eGFR_{CG}$, favoring F/TAF. Table 2 shows the mean changes at Weeks 48 and 96 for serum creatinine (a secondary endpoint at Week 48) and $eGFR_{CG}$.

Table 2: Mean Change from Baseline in Serum Creatinine and Estimated Glomerular Filtration Rate by Cockcroft-Gault Method at Weeks 48 and 96 (DISCOVER)

	F/TAF (N=2694)		F/TDF (N=2693)	
	N	Mean Change (SD)	N	Mean Change (SD)
Serum Creatinine (mg/dL)				
Week 48	N=2371	-0.01 (0.106)	N=2369	+0.01 (0.110)
Week 96	N=1210	+0.01 (0.115)	N=1264	+0.02 (0.116)
$eGFR_{CG}$ (mL/min)				
Week 48	N=2370	+2.0 (15.84)	N=2367	-2.0 (15.77)
Week 96	N=1208	-0.6 (18.25)	N=1262	-3.7 (16.90)

Source: FDA analysis of ADLB dataset from DISCOVER trial

Relevant to the discussion of tenofovir-associated renal toxicity is the assessment of biomarkers specific to tubular function. As previously noted, the DISCOVER trial had three such secondary endpoints, each assessed at Week 48: percentage change from baseline in urine beta-2-microglobulin to creatinine ratio, percentage change from baseline in urine RBP to creatinine ratio, and distribution of urine protein and UPCR categories. For each of these measures, there were statistically significant differences between the groups favoring F/TAF. With respect to changes from baseline in UPCR categories, as shown in Table 3, 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 numbers of subjects with UPCR > 200 mg/g at baseline or during the study were small and only the Week 48 differences were statistically significant.

Table 3: Shift Table of UPCR Category (≤200 vs 200 mg/g) by Baseline Category (DISCOVER)

	Number (%) of Subjects†			
	F/TAF		F/TDF	
Baseline	**≤200 mg/g** (N=2662)	**>200 mg/g*** (N=25)	**≤200 mg/g** (N=2657)	**>200 mg/g*** (N=25)
Week 48	**N=2335**	**N=21**	**N=2331**	**N=18**
≤200 mg/g	2318 (99)	12 (57)	2296 (98)	8 (44)
*>200 mg/g**	17 (1)	9 (43)	35 (2)	10 (56)
Week 96	**N=1172**	**N=14**	**N=1228**	**N=11**
≤200 mg/g	1158 (99)	10 (71)	1213 (99)	4 (36)
*>200 mg/g**	14 (1)	4 (29)	15 (1)	7 (64)

* Includes subjects with UPCR >200 mg/g and urine protein ≥4 mg/dL

† The denominator for percentages is the number of subjects with nonmissing values at baseline and postbaseline visit. Subjects with missing data at either baseline or postbaseline visit are not shown.

Source: FDA analysis of ADLB dataset from DISCOVER trial

The majority of subjects did not experience treatment-emergent proteinuria and most of the observed proteinuria was Grade 1 (1+ by urine dipstick). The percentage of subjects with Grade 1 proteinuria was higher in the F/TDF arm compared with the F/TAF arm (22% vs. 19%, respectively), although the percentage of subjects with Grade 2 proteinuria (2-3+ by dipstick) was equal in both arms (2%). There were no between-group differences in the frequency of other graded treatment-emergent renal laboratory abnormalities (Table 4).

Table 4: Treatment-emergent Renal-Associated Laboratory Abnormalities (DISCOVER)

	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)
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)

Denominator for percentage is the number of subjects with at least 1 postbaseline laboratory value.

Subjects were counted once for the maximum postbaseline severity.

Source: FDA analysis of ADLB dataset from DISCOVER trial

One subject in the F/TDF group was reported to have a nonserious event of Fanconi syndrome acquired on Study Day 421 that was considered related to study drug by the investigator and led to study drug discontinuation. Otherwise, there were no notable differences (i.e., no risk differences greater than 1%) between the groups in the incidence or types of renal-associated TEAEs. Based on a selection of MedDRA Preferred Terms from the 'Renal and urinary disorders' and 'Investigations' System Organ Class (excluding renal neoplasms, vascular and ischemic events, lithiasis, and obstructive disorders), renal-associated TEAEs were reported in 3% and 4% of F/TAF and F/TDF subjects, respectively (Table 5).

Table 5: Selected Renal-associated Treatment-emergent Adverse Events (DISCOVER)

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

Source: FDA analysis of ADAE dataset from DISCOVER trial

Serious renal-associated adverse events included 5 events of acute kidney injury and 1 event of nephrotic syndrome in the F/TAF arm, and 2 events of acute kidney injury in the F/TDF group.

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 6.

Table 6: Renal-associated Treatment-emergent Adverse Events Leading to Study Drug Discontinuation (DISCOVER)

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: FDA analysis of ADAE dataset from DISCOVER trial

Likewise, an equal percentage (0.2%) of subjects in each arm interrupted study drug due to a renal adverse event. TEAEs that led to study drug interruption and were reported in at least two subjects were acute kidney injury (F/TAF 4 [0.2%], F/TDF 1 [0.04%]) and renal impairment (F/TAF 0, F/TDF 2 [0.1%]).

In summary, interim results from the DISCOVER trial indicate that use of F/TAF as PrEP has favorable effects on biomarkers of renal tubular function relative to F/TDF at 48 weeks, but the clinical impact of these differences is less clear as the incidence of renal-associated adverse events, serious adverse events or adverse events leading to drug discontinuation, and of graded laboratory abnormalities, was comparable between the two treatment groups.

Bone Safety

Within the DXA substudy (n= 398; median age 37), subjects randomized to F/TAF showed slight mean percentage increases in BMD at the hip and spine at Weeks 48 and 96 (observed data), whereas those randomized to F/TDF showed mild but significant decreases at both anatomical sites (Table 7).

Table 7: Percentage Change from Baseline in Hip and Spine BMD at Weeks 48 and 96, Observed Data (DISCOVER)

	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	+0.183 (2.384)	-0.988 (2.435)
Week 96	N=100	N=105
Mean (SD) % Change from Baseline	+0.424 (2.612)	-1.202 (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	+0.496 (2.988)	-1.123 (2.945)
Week 96	N=100	N=112
Mean (SD) % Change from Baseline	+0.877 (3.143)	-1.248 (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: FDA analysis of ADDXA dataset from DISCOVER trial

In the subgroup of subjects less than 25 years of age, the differences between F/TAF and F/TDF in BMD changes at the hip and spine were statistically significant at Week 48 but not at Week 96; however, the sample size for this cohort was small (n=39).

Categorical analyses of the BMD percentage changes from baseline confirmed the differences between the groups noted above (Table 8).

Table 8: Categorical Distribution of Percentage Changes in Hip and Spine BMD at Weeks 48 and 96 (DISCOVER)

		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)
	≥ 3% Increase from Baseline	14/158 (9)	10/158 (6)
Week 96	No Decrease from Baseline	57/100 (57)	40/105 (38)
	≥ 3% Decrease from Baseline	5/100 (5)	22/105 (21)
	≥ 3% Increase from Baseline	12/100 (12)	4/105 (4)
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)
	≥ 3% Increase from Baseline	27/159 (17)	15/160 (9)
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: FDA analysis of ADDXA dataset from DISCOVER trial

With respect to clinical events, however, there were no discernable differences between the treatment groups in the frequency or types of fracture events or other events related to bone health. Fracture events were reported in 2% of subjects in each treatment group; the majority (91%) of fractures 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 had pathological fractures as determined by blinded medical monitor assessment (1 cervical vertebral fracture in F/TAF group, and 1 shoulder fracture and 1

metatarsal fracture in the F/TDF group). None of the pathological fractures were considered serious or related to study drug, and none led to study drug discontinuation. In all three cases of pathological fracture, there were confounding factors that may provide alternative etiology for the event; however, none of these subjects was included in the DXA substudy, so changes in BMD were not assessed.

Table 9 summarizes the fracture events reported in the DISCOVER trial. In addition, other TEAEs related to nonspecific back and limb pain are included, as some of these can be associated with osteomalacia in adults {Gifre et al. 2011}. Also included are terms related to BMD, osteopenia, and osteoporosis, as well as the standardized MedDRA queries (SMQs) for the latter two conditions.

Table 9: Treatment-emergent Adverse Events Related to Bone Safety (DISCOVER)

	MedDRA Preferred Term	Number (%) of Subjects	
		F/TAF (N=2694)	F/TDF (N=2693)
All fractures		53 (2)	53 (2)
All 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: FDA analysis of ADAE dataset from DISCOVER trial

As shown in Table 9, there were no between-group differences in the incidence of any of these events. All TEAEs of bone density decreased, bone loss, osteopenia and osteoporosis were mild or moderate in severity. Study drug was discontinued in four subjects, two for osteoporosis in the F/TAF group and two for back pain (1 per arm). Lastly, the number of subjects taking or initiating osteoporosis medications was minimal (n=5) and balanced between arms.

In summary, DXA scan results from the DISCOVER trial confirm the known differences between F/TAF and F/TDF with respect to BMD changes. The relevance of these laboratory findings to clinical outcomes remains unclear as there were no notable differences between the treatment groups with respect to fracture rates or the reporting of other events related to bone health.

Fasting Serum Lipids

In the DISCOVER trial, subjects randomized to F/TDF had greater decreases from baseline in serum fasting lipid levels at Weeks 48 and 96 compared to those who received F/TAF (Table 10); however, no within-group or between-group differences were noted for changes in the total cholesterol to HDL ratio, which is associated with cardiovascular disease risk.

Table 10: Median Change from Baseline in Fasting Lipids (DISCOVER)

LIPID PARAMETER	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	0.106	1188	0.115
	Change at Week 96	573	0.028	582	-0.013
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: FDA analysis of ADLB dataset from DISCOVER trial

Subjects in the F/TAF group also had a higher incidence of treatment-emergent elevations in fasting lipid abnormalities, as per the Applicant's toxicity grading scale (Table 11).

Table 11: Treatment-emergent Fasting Lipid Laboratory Abnormalities (DISCOVER)

	F/TAF	F/TDF
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)

Source: FDA analysis of ADLB dataset from DISCOVER trial

Lastly, in a categorical analysis based on LDL classifications from the National Cholesterol Education Program {National Institutes of Health (NIH) 2001}, subjects in the F/TAF group generally had worsening of LDL classification at Weeks 48 and 96 compared with subjects in the F/TDF group, who tended to have improvements (Table 12).

Table 12: Shift Table of Fasting LDL Classification by Baseline Category (DISCOVER)

	F/TAF (N=2694)				F/TDF (N=2693)			
	<100 (N=720)	100-159 (N=629)	160-190 (N=63)	>190 (N=11)	<100 (N=721)	100-159 (N=656)	160-190 (N=67)	>190 (N=17)
Week 48								
<100	418 (73)	126 (24)	1 (2)	1 (11)	487 (84)	192 (36)	1 (3)	2 (14)
100-159	154 (27)	371 (71)	24 (38)	0	95 (16)	325 (61)	29 (76)	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								
<100	202 (76)	81 (29)	2 (10)	0	247 (87)	104 (39)	2 (10)	0
100-159	63 (23)	186 (66)	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	5 (2)	2 (10)	1 (50)	0	1 (<1)	0	0

Source: FDA analysis of ADLB dataset from DISCOVER trial

The increases in fasting lipid parameters observed in the F/TAF group were not associated with any differences in cardiovascular or cerebrovascular events. However, the number and percentage of subjects who initiated lipid-modifying agents during the trial was two-fold higher in the F/TAF group compared with the F/TDF group (43 [1.6%] vs. 21 [0.8%], respectively), a difference that was statistically significant per the Applicant (p=0.008).

Summary of Safety

The safety data from the DISCOVER trial are consistent with previous trials of TAF that show improved measures of renal tubular function (as demonstrated by differences in renal biomarkers over time) and minimal impact on bone mineral density (as seen on DXA imaging) with TAF dosing relative to TDF. While these subclinical differences are significant, and favor Descovy, the clinical advantage of F/TAF is less clear in the context of a 96-week study, where there were no differences between F/TAF and F/TDF in the frequency or types of clinical adverse events related to renal or bone safety, or in the frequency or severity of abnormalities for laboratory tests commonly monitored in clinical practice. Indeed, the clinical safety profile of F/TAF and F/TDF were remarkably similar in this trial with respect to common adverse events, serious adverse events or adverse events leading to drug discontinuation (the latter two of which occurred at low rates in both arms). 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 the DISCOVER trial among subjects taking F/TAF compared with F/TDF. While these findings were not associated with greater cardiovascular risk, they may have led to a greater number of participants in the F/TAF group initiating lipid-lowering therapy.

b. Cisgender Women

The efficacy and safety of Descovy for HIV PrEP in cisgender women have not been evaluated. The Applicant proposes to extrapolate the efficacy and safety of Descovy for HIV PrEP to cisgender women

using PK, safety, and efficacy data collected from clinical trials evaluating TAF- or TDF-containing regimens as follows.

Efficacy

The Applicant proposed two approaches to extrapolate efficacy to support a PrEP indication for F/TAF in cisgender women. The first approach is to extrapolate efficacy from MSM/TGW receiving F/TAF in the DISCOVER trial by demonstrating comparable systemic PK exposures (TAF in plasma and TFV-DP in PBMCs) between MSM/TGW and cisgender women. However, this approach may not be sufficient to ensure the efficacy of F/TAF in cisgender women for the following reasons: 1) mucosal drug concentrations appear to be important to PrEP efficacy (see Section 2.b.) and systemic drug exposures may not correlate with mucosal tissue concentrations, and 2) across the PrEP clinical trials of Truvada, differences in efficacy were observed between men and cisgender women despite comparable systemic exposures (tenofovir (TFV) in plasma and TFV-DP in PBMCs). As part of its rationale for utilizing systemic drug exposure data to support a PrEP indication in cisgender women, the Applicant also states that TAF can quickly (within 2-3 hours following a single dose) achieve TFV-DP concentrations of 40 fmol per million cells in PBMCs of both men and women, a clinical threshold demonstrating a level of adherence reportedly associated with a greater than 90% reduction in HIV acquisition (EC_{90}) in prior PrEP trials of Truvada {Anderson et al. 2012a; Anderson et al. 2012b}. However, while this target concentration may be valid for MSM receiving F/TDF, it may not apply to F/TAF due to the differences between TDF and TAF in the correlation between PBMCs and mucosal tissue concentrations for TFV-DP.

The other approach is to extrapolate efficacy from the successful trial of Truvada in cisgender women (i.e., Partners PrEP). For this approach, efficacy would be extrapolated by demonstrating comparable or higher TFV-DP concentrations in PBMCs and cervicovaginal mucosal tissues. Since it has already been demonstrated that TFV-DP concentrations in PBMCs are 4-7-fold higher following the administration of TAF compared with TDF, the extrapolation would need to demonstrate comparable or higher exposures of TFV-DP in cervicovaginal tissues following the administration of F/TAF compared to F/TDF. 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"* (CONRAD Protocol A15-137) {Schwartz et al. 2018}.

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 F/TDF or F/TAF in HIV-negative, healthy adult female volunteers. Treatments were given as shown below.

- 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 samples were collected to determine the PK of TAF, TFV, FTC and their intracellular active metabolites:

- Plasma for TAF, TFV, and FTC
- PBMC for TFV-DP, FTC-TP, dATP, and 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.

Of note, tissue samples were collected in a sparse manner and each subject provided tissue samples at only one given time point; thus, tissue PK parameters for an individual subject or correlations between samples collected at different time points cannot be determined.

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. In a separate single-dose study {Cottrell et al. 2017}, a high percentage (87.5%) of BLQ results were also observed for female genital tract tissues following administration of TAF. Therefore, it is not known whether F/TAF provides higher TFV-DP concentrations in vaginal tissues following single-dose administration relative to F/TDF.

Following 14-day 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 13). 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 13: 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 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 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 with daily dosing at steady-state, 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.

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

Safety

The long-term safety of Descovy in HIV-negative cisgender women has not been evaluated, but long-term safety data for FTC and TAF are available in HIV-infected women from various HIV treatment trials of F/TAF-containing products, such as Genvoya® (elvitegravir/cobicistat/F/TAF) and Biktarvy® (bictegravir/F/TAF). Further, the safety of Descovy has been determined in HIV-uninfected MSM/TGW in the DISCOVER trial (see section 3a). Based on pooled PK data across trials, neither sex nor HIV-1 infection status has any clinically relevant impact on the systemic exposures of TAF or FTC. Therefore, based on the overall safety profile of Descovy observed across multiple trials and PK similarities noted among HIV-uninfected women, HIV-uninfected men, and HIV-infected women, it is reasonable to conclude that the existing safety database for Descovy could be used to support its use as PrEP in cisgender women at risk of HIV acquisition.

c. Adolescents

Clinical trials to evaluate Descovy PrEP efficacy, safety, and adherence in adolescents have not been conducted. The Applicant proposes to extrapolate efficacy data from the DISCOVER trial in MSM/TGW to support a PrEP indication in adolescents. While no PK studies were conducted in adolescents for this specific indication, available data suggest no clinically relevant differences in the PK of plasma FTC, plasma TAF, or PBMC-associated TFV-DP between HIV-infected adolescents weighing at least 35 kg and HIV-infected adults. Likewise, there are no clinically relevant PK differences for FTC and TAF and their active metabolites between HIV-infected adults and uninfected adults. Therefore, it is reasonable to expect that PK parameters will be similar between HIV-uninfected adolescents and HIV-uninfected adults, thus allowing for extrapolation of adult efficacy. Safety in adolescents is supported by findings

from the DISCOVER trial in HIV-uninfected MSM/TGW and other trials of F/TAF in HIV-infected adolescents. Taken together, based on pharmacological and clinical considerations, it is reasonable to expand the PrEP indication to MSM/TGW adolescents weighing at least 35 kg. As discussed in Section 3b, however, efficacy data from MSM/TGW cannot be extrapolated to cisgender women based solely on the available PK data, and thus the results from the DISCOVER trial cannot be extrapolated to female adolescents.

Adherence to PrEP in adolescents has previously been shown to wane over time, particularly when clinic visits become less frequent {Hosek et al. 2017}. Labeling for Truvada suggests that adolescents may benefit from more frequent visits and counseling {Gilead Sciences Inc. 2018}. Similar adherence support would likely be recommended for use of Descovy for PrEP in an adolescent population.

4. Summary

Clinical trial data from the DISCOVER trial submitted in support of this application show that Descovy and Truvada were similar in reducing HIV-1 infection in MSM and TGW. Although the number of HIV-1 infections observed in this trial was low, noninferiority of Descovy to Truvada was still demonstrated. One potential concern raised by such a low number of primary endpoint events is whether the trial was conducted in an appropriate population at substantial risk for HIV-1 infection, as it would be difficult to demonstrate a treatment effect in a low-risk population. Given the selection of study site locations, the risk behaviors reported by participants both at baseline and during the trial, the high incidence of STIs diagnosed during the trial, and the availability of surveillance data that show high background HIV transmission rates at the U.S. site locations, it seems unlikely that the DISCOVER trial was conducted in a population not at substantial risk. Therefore, one could hypothesize that the low HIV infection rate observed in the trial is due to the high efficacy of both Descovy and Truvada in preventing HIV-1 infection when adherence is also high, as was the case in this trial.

While the demographics of the DISCOVER trial participants are more reflective of current PrEP users (i.e., white, educated, MSM in their 30s), rather than the minority U.S. populations currently most at risk of HIV-1 infection, the sexual risk behaviors and STI rates reported in this study cohort suggest a population at high risk of HIV-1 infection. In addition, although unprotected receptive anal intercourse was reported by most participants, 16% of participants had documented urethral infections with gonorrhea or chlamydia during the trial suggesting that unprotected insertive intercourse was also occurring. Therefore, the efficacy results from the DISCOVER trial might be considered relevant to a broader, more diverse male population.

The safety of Descovy for a PrEP indication is supported by results of the DISCOVER trial as well as extensive safety data with F/TAF from clinical trials in HIV-infected subjects. In the DISCOVER trial, Descovy was safe and well tolerated in an HIV-uninfected population. Consistent with previous trials, administration of F/TAF in this trial resulted in improved biomarkers of renal function and bone mineral density as seen on DXA scan compared with F/TDF. The safety profile of Descovy as it pertains to clinical events, however, was similar to that of Truvada. The most common non-infectious adverse events

(diarrhea, nausea, headache, and fatigue) and drug reactions (predominantly GI-related) were the same in both treatment groups, and there was no difference regarding the incidence, types, severity or timing of most other adverse events, including serious events and those leading to drug discontinuation. Also consistent with previous trials, the use of Descovy resulted in a higher incidence of elevated fasting lipids compared to Truvada, with twice as many subjects in the Descovy arm initiating lipid-lowering agents during the trial (although the percentage was low at 2%).

There are no clinical trial data available to directly support the use of Descovy as PrEP in cisgender women or adolescents. While an adolescent indication can be readily supported by extrapolation of adult efficacy data, an extrapolation approach to support an indication in cisgender women is predicated upon which drug exposures are considered most relevant to PrEP efficacy, systemic or local mucosal tissue drug concentrations. There is a general lack of consensus regarding this issue. Therefore, in the absence of clinical trial data in cisgender women, the approach taken by the FDA has been to request sufficient PK data to assess both systemic PK and local tissue concentrations. The systemic PK data from the DISCOVER trial demonstrate that oral administration of Descovy results in several-fold higher intracellular concentrations of TFV-DP in PBMCs as compared with Truvada, consistent with previous trials of TAF. As such, a systemic PK approach would be feasible. However, the cervicovaginal PK data from Study A15-137 are severely compromised by the large amount of unquantifiable measurements, rendering the data largely uninterpretable. As such, bridging to Truvada efficacy through a local tissue PK link is not possible. The present application is therefore limited to just systemic drug exposure to potentially support a PrEP indication in cisgender women.

5. Points for Advisory Committee Consideration

a. Do the safety and efficacy data from the DISCOVER trial support the approval of Descovy for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually-acquired HIV-1 infection in men and transgender women who have sex with men? If not, what additional studies/trials are needed?

b. 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 expansion of the Descovy PrEP indication to include cisgender women? If not what additional studies/trials are needed? If clinical trials are needed, please comment on trial designs that would be adequate to expand the indication.

c. Please discuss whether the data from the DISCOVER trial are relevant to at-risk men who practice insertive vaginal sex with cisgender women?

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