DESCOVY®
FOR HIV PRE-EXPOSURE PROPHYLAXIS

Antimicrobial Drugs
Advisory Committee Meeting
Briefing Document

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EXECUTIVE OVERVIEW

Human immunodeficiency virus type 1 (HIV; HIV-1) infection is a global epidemic, with an estimated 36.9 million people worldwide and 1.1 million people in the United States (US) living with the disease. Since the early days of the HIV/AIDS epidemic, advancements in antiretroviral treatment have transformed HIV into a manageable chronic condition for many people; however, there is still no cure, and maintaining viral suppression requires lifelong therapy. The rate of new HIV infections has remained stable in the US since 2013, with approximately 39,000 people newly diagnosed each year. Although stable overall, the infection rate has increased in some groups, including young men ages 25 to 34 years who have sex with men, and men of African American race or Latinx ethnicity. These statistics underscore the necessity for additional HIV prevention strategies in the US so that individuals who are at risk of HIV infection can protect themselves.

PrEP, or pre-exposure prophylaxis, is a biomedical strategy that effectively prevents HIV-uninfected individuals from acquiring the infection. Truvada®, a fixed-dose combination tablet comprised of the nucleoside analog reverse transcriptase inhibitors (NRTIs) emtricitabine (FTC, F) and tenofovir disoproxil fumarate (TDF), was initially approved as part of a complete regimen for the treatment of HIV infection in the US in 2004 and subsequently for a PrEP indication in 2012. The 2-drug combination has additive effects on efficacy in HIV prevention in both animal and human studies, compared with either agent alone. Truvada (and generic versions) is currently the only approved product for PrEP worldwide.

Truvada is highly effective for PrEP when used daily, with a relative rate of HIV risk reduction of up to 92% among individuals with detectable drug levels in prior clinical studies. In regions where PrEP uptake is high, declines in HIV incidence have been observed. An analysis of the impact of PrEP in the US conducted by the US Centers for Disease Control and Prevention (CDC), Emory University, and Gilead clearly demonstrated that US states with higher PrEP uptake have more substantial reductions in new HIV diagnoses, and importantly, that the impact of PrEP use is independent of rates of viral suppression (treatment as prevention [TasP]) among people who are living with HIV in those states.

While Truvada for PrEP effectively prevents HIV infection, the uptake of PrEP in the US is low as compared with the number of individuals who should be using it. The CDC estimates that there are 1.1 million people in the US with an indication for PrEP use, yet just over 130,000 (11.8%) of those with a CDC-defined PrEP indication were using it in the first half of 2019. To address this, Gilead and many national and local prevention service organizations continue to work to improve PrEP awareness, provide risk reduction education, reduce stigma, increase engagement of individuals at risk of HIV infection in healthcare, and support reduced or no cost drug availability programs for those needing assistance.

Surveys of healthcare providers and of current and lapsed Truvada for PrEP users demonstrate that concern for adverse effects is one of the strongest deterrents to initiation of PrEP and for persistence of PrEP use.
Truvada is an oral once-daily medication that was approved for use in chronic HIV treatment in 2004, and over 14 million person-years of exposure have accumulated. These data provide a comprehensive understanding of the safety profile, and while Truvada is generally well tolerated, both clinical trial data and real-world experience show that use of Truvada is associated with safety risks, particularly in kidney and bone.

Truvada contains FTC 200 mg and TDF 300 mg. After absorption from the gut, the TDF prodrug is hydrolyzed to tenofovir (TFV) which circulates in plasma. It is the circulating levels of TFV that cause off-target side effects and are responsible for the safety outcomes in users of TDF-based regimens like Truvada. Once plasma TFV is taken up by plasma peripheral blood mononuclear cells (PBMCs), TFV is diphosphorylated to its active form TFV diphosphate (TFV-DP), and it is TFV-DP that effectively blocks HIV-1 virus replication.

Descovy® is an oral once-daily medication that was approved for use in chronic HIV treatment in 2016, and over 1.3 million person-years of exposure have accumulated. Like Truvada, Descovy is indicated for use as part of a complete regimen for treatment of HIV infection.

Descovy is a fixed-dosed combination tablet containing FTC 200 mg and the NRTI, tenofovir alafenamide (TAF) 25 mg. The TAF prodrug is also hydrolyzed to TFV in plasma but this occurs much more slowly so that plasma TFV levels are more than 90% lower in TAF users than in TDF users. The lower plasma TFV levels that occur with TAF use result in less off-target bone and renal side effects (including drug-related discontinuations) and significantly improved bone and renal safety outcomes.

From an efficacy perspective, TAF use has consistently shown a 4- to 7-fold increase in TFV-DP levels as compared to TDF use. In a 10-day monotherapy study, TAF was associated with increased HIV viral load reduction (TAF 25 mg 1.5 log vs TDF 300 mg 1.0 log). In addition, TAF administration results in high TFV-DP levels more quickly than occurs with TDF administration. Recent pharmacokinetic data from healthy volunteers demonstrate that oral administration of TAF 25 mg leads to TFV-DP concentrations in PBMCs above 40 fmol per million cells, the threshold associated with a ≥ 90% reduction in HIV acquisition (90% effective concentration [EC90]) in prior Truvada for PrEP studies, within 2 to 3 hours after a single dose. In contrast, oral administration of TDF 300 mg requires 3 to 4 days for TFV-DP concentrations to reach the 40 fmol per million cell threshold. After once-daily dosing to steady state and then stopping further dosing, median TFV-DP concentrations remain above 40 fmol per million cells for 16 days with TAF, but just 9 to 10 days with TDF.

Clinical data with TAF- and TDF-based regimens are consistent with the pharmacokinetic attributes of both drugs.

From a general safety perspective, TAF and TDF have comparable results. In contrast, clinical TAF use has consistently shown better bone and renal safety results. These significant improvements for TAF users include less impact on bone mineral density (BMD), less impact on serum creatinine and creatinine clearance, less urine protein loss (including proximal tubular proteins), and fewer renal drug-related discontinuations.
In terms of their antiviral effect, TAF and TDF have comparable efficacy results in chronic HIV treatment studies. TAF-based regimens have been consistently shown to be statistically noninferior to TDF-based regimens for use in chronic HIV treatment. The lack of statistically better efficacy results in TAF users is likely due to the concurrent use of a potent third drug for both regimens, thereby equalizing the efficacy endpoint results.

TAF-containing products have been used by more than 1.1 million people living with HIV worldwide, with a consistently favorable safety profile. Based on both the clinical trial data and real-world use, TAF has replaced TDF as part of the backbone of many chronic treatment regimens and is recommended by leading treatment guidelines. TAF-containing regimens are used internationally and considered to be part of the standard of care in chronic HIV treatment regimens.

Given the favorable pharmacokinetic characteristics of TAF and the extensive clinical safety and efficacy data in chronic HIV treatment, Gilead conducted the Descovy for PrEP development program, including the Phase 3 DISCOVER study, and is providing a set of clinical and pharmacokinetic bridging data, with the intention of registering Descovy for the prevention of HIV infection.

The DISCOVER Study (GS-US-412-2055)

The DISCOVER study is an ongoing 96-week study of once-daily Descovy versus Truvada for use as HIV PrEP. The study is being conducted in cis-men (gender identity is the same as their assigned sex at birth) and transgender women (TGW) who have sex with men. Participants were randomized to receive either Descovy or Truvada (1:1 ratio) in a blinded fashion.

Eligibility for participation in the study was based on being at high sexual risk of acquiring HIV infection. Along with a negative HIV test at the eligibility screening visit, participants must have reported at least 2 episodes of condomless anal sex with at least 2 unique partners in the 12 weeks prior to screening, or had been diagnosed with rectal gonorrhea, rectal chlamydia, or syphilis in the 24 weeks prior to screening.

Study sites were selected to participate in the DISCOVER study based on the following criteria: presence in a community with high background HIV incidence, the ability to enroll individuals with significant sexual risk for HIV acquisition, the ability to enroll people of color, knowledge and experience working with TGW, and the ability for the investigator and study staff to meet all study requirements and conduct the study with high quality.

The study was designed in collaboration with community representatives and with US Food and Drug Administration (FDA) input. Gilead followed guidelines for Good Participatory Practices (GPP), Good Clinical Practices (GCP), and routine Gilead clinical trial quality assurance standards in the design, conduct, and analysis of the study. The Gilead study team incorporated considerable feedback from the community during protocol development, and an independent data monitoring committee (IDMC) was convened to meet at prespecified points during the study in order to review unblinded data.
The primary efficacy endpoint was the HIV incidence rate per 100 person-years in the study. The efficacy analysis was time-driven (not event driven) and was conducted once all study participants completed 48 weeks and half of participants completed 96 weeks.

To assess noninferiority of Descovy to Truvada, the HIV incidence rates for the 2 groups were tested using a rate ratio in which the incidence rate in the Descovy group was divided by the rate in the Truvada group. The prespecified noninferiority margin of 1.62 was based on equal weighting of the efficacy results from 3 prior PrEP studies (ie, iPrEx, PROUD, IPERGAY). Using these earlier data, noninferiority of Descovy to Truvada would be established if the upper bound of the 95% confidence interval (CI) surrounding the rate ratio was less than 1.62.

To determine ongoing risk of HIV infection at each study visit, each study participant was tested for sexually transmitted infections (STIs) (gonorrhea and chlamydia) from 3 anatomic sites (oropharynx, urine, and rectum), and all participants had serologic testing for syphilis. In addition, all participants completed a confidential questionnaire at each visit, asking about types of sexual behavior, frequency of sexual encounters, number of unique sex partners, condom use, and recent study drug adherence. Staff at study sites provided risk reduction education, and condoms and lubricant were available for study participants.

Because of the importance of adherence in HIV prevention, multiple adherence tests were used. Subjective assessments of adherence were self-reported adherence and pill counts in returned study drug bottles. Objective adherence assessments included measurement of study drug levels. Study staff provided adherence support and participants could opt to receive daily text messaging reminders to take their medications.

To assess the relationship of adherence with efficacy in the study, a case-control analysis was conducted to compare levels of TFV-DP in red blood cells (RBC) from dried blood spot (DBS) samples (DBS testing) in participants who became infected with HIV during the study (“cases”) and matched participants who were not infected with HIV (“controls”).

In addition to standard clinical safety evaluations, bone safety was assessed in a subset of participants, while renal laboratory parameters were evaluated in all participants. Using an alpha-controlled analysis cascade, 6 prespecified secondary safety endpoints (2 bone; 4 renal) were analyzed to compare bone and renal safety between participants receiving Descovy and Truvada. In a subset of the overall study population, BMD was assessed using dual-energy x-ray absorptiometry (DXA) scanning at the hip and spine. Renal safety was assessed by measurement of protein in urine (including proximal renal tubular proteins), and calculation of creatinine clearance.

**DISCOVER Study Population**

Screening for DISCOVER began in September of 2016 and enrollment was complete in May 2017.

A total of 5387 participants from 11 countries in the US, Canada, and Europe were randomized and enrolled into the DISCOVER study, and received at least 1 dose of study drug, with 2694 in the Descovy group and 2693 in the Truvada group.
As of the primary analysis data cut date, 83% to 84% of participants were still on study drug. The majority of participants who prematurely discontinued from the study were lost to follow-up or discontinued due to participant decision. A total of 1.3% to 1.7% of study participants discontinued study drug due to an adverse safety event.

Demographics were similar across the groups. The median age was 34 years. Most participants (5313; 98.6%) were cis-men, and 74 (1.4%) self-identified as TGW. Racially, 4511 (83.9%) were white, 474 (8.8%) were of black or mixed black race, and 233 (4.3%) were of Asian race. A total of 1318 (24.5%) participants were of Hispanic or Latinx ethnicity.

All participants qualified for participation on the basis of sexual risk, which was similar for the 2 groups. A total of 61.3% of participants reported having had 2 or more episodes of condomless receptive anal sex with at least 2 unique partners prior to screening, and 9.9%, 12.5%, and 9.2% had a recent medical history of rectal gonorrhea, rectal chlamydia, or syphilis, respectively.

At baseline, 905 participants (16.8%) were using Truvada for PrEP, and 1247 participants (23.1%) had previously used Truvada for PrEP. Two-thirds of participants reported recreational drug use (many as part of chemsex), and approximately one-quarter reported binge drinking.

**DISCOVER Efficacy Results**

Adherence to study drug was high throughout the study. In both groups, median adherence by pill counts was 98% and median self-reported adherence was 100%. Most participants had levels of TFV-DP in RBC from DBS consistent with study drug dosing at least 4 days per week on average, the Truvada dosing requirement associated with > 90% reduction in HIV incidence.

At the prespecified primary efficacy endpoint analysis, 22 HIV infections were diagnosed, as follows: 7 in the Descovy group (incidence rate = 0.16 infections per 100 person-years) and 15 in the Truvada group (incidence rate = 0.34 infections per 100 person-years).

Noninferiority was assessed using the incidence rate ratio (Descovy incidence rate over Truvada incidence rate). The incidence rate ratio was 0.47 with a 95% CI of 0.19 to 1.15. As the upper bound of the 2-sided 95% CI for the incidence rate ratio was less than the noninferiority margin of 1.62, noninferiority of Descovy to Truvada was demonstrated. This incidence rate ratio of 0.47 represents a 53% reduction in HIV incidence for Descovy over Truvada.

Assessment of TFV-DP in RBCs using DBS testing provides a validated method to evaluate drug adherence data over the approximately 8 weeks before sample collection. Seventeen of the 22 HIV diagnoses were due to infections that occurred on study. Of these 17 HIV diagnoses, 15 individuals had TFV-DP levels by DBS testing that were very low or undetectable (5 in the Descovy group and 10 in the Truvada group) at the HIV diagnosis visit. One individual in the Descovy group had a low to medium level of TFV-DP, and 1 individual in the Truvada group had a high level of TFV-DP that had been imputed from TFV-DP levels at the visit prior to the visit of HIV diagnosis.
Five of the 22 HIV diagnoses occurred in participants who were likely to have become infected before starting study drug. Of these 5 suspected baseline infections, 1 was in the Descovy group and 4 were in the Truvada group.

An efficacy sensitivity analysis was conducted that excluded these 5 participants, leaving modified HIV incidence rates of 0.14 infections per 100 person-years in the Descovy group and 0.25 infections per 100 person-years in the Truvada group (rate ratio = 0.55; 95% CI: 0.20 to 1.48). Thus, the sensitivity analysis again demonstrated that Descovy was noninferior to Truvada, as the upper bound of the 2-sided 95% CI of the rate ratio was still less than 1.62.

There were no statistically significant differences in efficacy across any subgroups based on demographics or baseline characteristics.

Because both study groups received active treatment and no placebo group was used in DISCOVER, a direct comparison of the efficacy data in DISCOVER with efficacy data from the prior placebo-controlled randomized clinical trials could not be performed. Nonetheless, a background HIV infection rate (or placebo rate) can be estimated using 2 techniques:

1) Rectal gonorrhea rates have been shown to strongly correlate with HIV infection rates in men not using PrEP. Given the DISCOVER rectal gonorrhea rates of 22 infections per 100 person-years in the Descovy group and 21 infections per 100 person-years in the Truvada group, the predicted HIV incidence rates in DISCOVER that would have occurred in the absence of PrEP use had participants not been taking Descovy or Truvada based on this published correlation were 6.61 (95% CI: 3.92, 9.29) infections per 100 person-years in the Descovy group and 6.36 (95% CI: 3.69, 9.03) infections per 100 person-years in the Truvada group.

2) A background rate of HIV transmission in US geographic areas with DISCOVER sites was calculated using HIV surveillance data as reported to the CDC across metropolitan statistical areas in the US. The HIV infection rate in PrEP-eligible US MSM not taking PrEP (and not part of DISCOVER) in these areas was calculated to be 4.02 (95% CI: 3.96, 4.09) infections per 100 person-years of follow-up.

Given the actual HIV incidence rates in DISCOVER of 0.16 and 0.34 per 100 person-years for the 2 groups, both of these indirect comparisons independently confirm that significantly higher HIV incidence rates would have occurred among participants in the DISCOVER study had they not been taking either Descovy or Truvada.

DISCOVER Safety Results

In the DISCOVER study, both Descovy and Truvada were safe and well tolerated in over 8658 person-years of exposure overall, with low rates of serious adverse events (SAEs) and adverse event (AE)-related discontinuations. The type, frequency, and severity of reported AEs were similar between groups. Unlike studies of TAF and TDF in chronic HIV treatment, the most commonly reported AEs were STIs, reflective of the sexual behavior of study participants.
Descovy was superior to Truvada in all 6 secondary safety endpoints in the prespecified analysis cascade.

The 2 prespecified bone safety endpoints showed statistically significant differences favoring Descovy over Truvada through 48 weeks in the study. Those on Descovy had increases in spine and stable hip BMD, while those on Truvada had declines in BMD at both sites. In addition, on all 4 prespecified renal safety endpoints, those on Descovy had significantly less change in proteinuria and significantly improved renal function. Though not a part of the analysis cascade, those on Descovy also had fewer discontinuations due to renal AEs. There were no participants with Fanconi Syndrome in the Descovy group and one participant with Fanconi Syndrome in the Truvada group, who was discontinued from study drug.

Among the subset of study participants who were taking Truvada for PrEP at baseline, there were either statistically significant or numerical advantages for those in the Descovy group for each of the 6 prespecified secondary safety endpoints.

At study entry, DISCOVER participants reported a high level of sexual behavior associated with increased risk of HIV infection, and a low level of condom use. This resulted in a high STI rates, with a rectal gonorrhea infection rate of 21 to 22 infections per 100 person-years; a rectal chlamydia rate of 28 infections per 100 person-years, and a syphilis infection rate of 10 infections per 100 person-years. Moreover, of the 9 treatment-emergent AEs that occurred in at least 10% of study participants, 6 were STIs.

**Extrapolation of DISCOVER Data to Cis-Women and Adolescents**

For women in the US, HIV continues to be a public health concern. According to recent CDC estimates, 19% of new HIV infections in 2017 were in women, predominantly through heterosexual contact. The use of PrEP as part of an effective HIV prevention strategy in women is recommended for heterosexual women at risk of HIV in the CDC and American College of Obstetricians and Gynecologists (ACOG) clinical guidelines. Similarly, young persons (aged 13 to 24 years) comprised a large portion of new HIV infections in the US (approximately 21% per CDC estimates) predominantly through sexual contact (99% and 86% of new HIV infections among young men and women, respectively).

Although the DISCOVER study was conducted in men and TGW, the well-established pharmacokinetic, efficacy, and safety data generated across F/TAF-development programs support extrapolation of the DISCOVER study results to the important populations cis-women or adolescents. The extrapolation is supported by prior experience that demonstrates that HIV PrEP with Truvada is efficacious in these populations.

The pharmacokinetics of the components of Descovy are well characterized across several clinical development programs of F/TAF-containing products, with over 1.3 million person-years of exposure, including 203,000 person-years of exposure in women worldwide. Analyses have demonstrated that FTC, TAF, and TFV-DP pharmacokinetics are not affected by demographic factors, including biologic sex at birth, current gender identity, sexual orientation, HIV infection, or age. As such, pharmacokinetic results across clinical programs in men, women and adolescents, including pharmacokinetic data generated in the DISCOVER population, support
extrapolation of DISCOVER study efficacy data to cis-women and adolescents. The extrapolation is further supported by available data with Truvada that demonstrate comparable PrEP efficacy in men, women, and adolescents and additional pharmacokinetic data in female volunteers that demonstrate higher concentrations of TFV-DP in cervicovaginal tissues with Descovy compared to Truvada.

Further, safety data for Descovy observed across several large clinical development programs in (eg, Genvoya®, Biktarvy®, Odefsey®) men, women, and adolescents living with HIV form the basis for the characterization of safety of Descovy. Results from clinical studies are augmented by real-world experience of 202,538 person-years of experience in cis-women with FTC/TAF-containing products in the postmarketing setting for HIV treatment and hepatitis B virus treatment.

For both cis-women and adolescent populations, extensive safety experience with Descovy (and other TAF-based products) from clinical studies and real-world settings consistently demonstrate the safety advantages of TAF-based regimens over TDF-based regimens.

In analyses of Descovy-based regimens, FTC, TAF, and PBMC-associated TFV-DP pharmacokinetics are comparable between female and male healthy volunteers, adolescents, and participants in DISCOVER. FTC and TAF pharmacokinetics are also comparable between cis-women with HIV and healthy female volunteers. As a consequence, based on the pharmacokinetic bridges, the comparable clinical efficacy data, and comparable clinical safety data, the extrapolation of data from DISCOVER and other studies support the use of a safer and equally effective PrEP drug, Descovy in cis-women and adolescents.

**Executive Summary Conclusion**

The clinical advantages of TAF are based on the pharmacokinetic characteristics of the drug. Lower TFV levels in plasma lead to fewer off-target side effects and significantly less changes in renal and bone safety parameters. Higher TFV-DP levels in plasma PBMCs lead to more rapid, higher, and more sustained activity against HIV.

The DISCOVER study demonstrated the noninferiority of Descovy to Truvada in the prevention of HIV infection among men and TGW who have sex with men. The study population was at sustained, high risk for HIV infection. Low HIV incidence rates across both arms were observed, consistent with the high level of adherence to study drug and the effectiveness of the drugs used. As has been consistently demonstrated in other PrEP clinical studies, individuals with very low or undetectable drug levels are more likely to become infected with HIV, while those with adequate drug levels are protected. In DISCOVER a similar relationship between adherence and HIV infection was shown.

Based on this large, double-blind, randomized clinical study conducted in a population at substantial risk for HIV, the efficacy and safety data from the DISCOVER study demonstrate that Descovy is effective for HIV prevention and has an improved bone and renal safety profile compared with Truvada. Using extensive published clinical trial data and the findings from DISCOVER, along with a pharmacokinetic bridge, Gilead also proposes to include cis-women
and adolescents in this HIV prevention indication, important populations who deserve and may benefit from an equally efficacious and safer drug option for PrEP.

Gilead therefore proposes a new Descovy indication for HIV prevention. The availability of Descovy for PrEP will increase drug options for the prevention of HIV infection for men, women, and adolescents, and will contribute to the goal of preventing HIV in those at risk, and will contribute to the goal of reducing the global AIDS pandemic.

The proposed indication for Descovy is as follows:

- For PrEP to reduce the risk of sexually acquired HIV-1 in at risk adults and adolescents weighing at least 35 kg.

Gilead welcomes the opportunity to discuss the use of Descovy for PrEP at the 07 August 2019 FDA Advisory Committee meeting.
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GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACOG: American College of Obstetricians and Gynecologists
AE: adverse event
AIDS: acquired immunodeficiency syndrome
ANCOVA: analysis of covariance, a statistical test used to detect a difference between groups in a particular endpoint while controlling for the effects of confounding variables
ANOVA: analysis of variance, a statistical test used to detect differences between groups in a particular endpoint
AUC: area under the concentration versus time curve, a measure of the body’s exposure to a drug
AUC_{inf}: area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + \left( C_{last} / \lambda_z \right)$, a measure of the body’s total exposure to a drug from time of dosing to elimination
AUC_{last}: area under the concentration versus time curve from time zero to the last quantifiable concentration, a measure of the body’s exposure to a drug from time of dosing to the last measurable concentration
AUC_{tau}: area under the concentration versus time curve over the dosing interval, a measure of the body’s exposure to a drug through the dosing interval
AUDIT: Alcohol Use Disorders Identification Test, used during the DISCOVER study to collect data on the recreational drug and alcohol use history of participants
B/F/TAF: bictegravir/emtricitabine/tenofovir alafenamide (coformulated)
BMD: bone mineral density, a measure used to assess bone strength and risk of fractures
BVY: bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
CASI: computer-assisted self-interview, used during the DISCOVER study to collect data on sexual behavior and adherence by participants
CDC: Centers for Disease Control and Prevention
chemsex: sexual activity engaged in while under the influence of stimulant drugs
CI: confidence interval, a statistical term describing a range of values likely to contain the true value of a parameter of interest with a certain degree of confidence
cis-woman, cis-man: an individual whose gender identity is the same as their assigned sex at birth
C_{max}: maximum observed concentration of drug
COBI, C: cobicistat, a drug used in HIV treatment
CSR: clinical study report
C_{tau}: observed drug concentration at the end of the dosing interval
DBS, DBS testing: dried blood spot, used to measure levels of study drug in red blood cells to estimate adherence
DHHS: Department of Health and Human Services
DOT: directly observed therapy
DVY: emtricitabine/tenofovir alafenamide (coformulated; Descovy®), a fixed-dose combination drug used in HIV treatment
DXA: dual-energy x-ray absorptiometry, a test to measure bone mineral density (see also BMD)
EACS: European AIDS Clinical Society
EC_{90}: 90% effective concentration
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E/C/F/TAF elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
E/C/F/TDF elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
eGFR estimated glomerular filtration rate
eGFR_CG estimated glomerular filtration rate calculated using the Cockcroft-Gault equation, a measure used to assess kidney function
EVG, E elvitegravir, a drug used in HIV treatment
F/R/TAF emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®)
F/TAF emtricitabine/tenofovir alafenamide, a fixed-dose combination tablet consisting of 2 drugs used in HIV treatment (marketed as Descovy in the US)
F/TDF emtricitabine/tenofovir disoproxil fumarate, a fixed-dose combination tablet consisting of 2 drugs used in HIV treatment (marketed as Truvada in the US)
FAS Full Analysis Set, the primary analysis set for efficacy analyses
FDA Food and Drug Administration
FTC, F emtricitabine, a drug contained in Descovy and Truvada (see also DVY and TVD)
FTC-TP emtricitabine 5′-triphosphate, the active metabolite of emtricitabine (see also FTC)
GCP Good Clinical Practice
GEN elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
Gilead Gilead Sciences
GLSM geometric least-squares mean, estimated mean value based on a statistical model
GPP Good Participatory Practices
HBV hepatitis B virus
HIV human immunodeficiency virus
HIV-1 human immunodeficiency virus type 1
IAS International AIDS Society
ID identification (number)
IDMC independent data monitoring committee
INSTI integrase strand-transfer inhibitor, an HIV drug class
LGBT lesbian, gay, bisexual, and transgender
LSM least-squares mean, estimated mean value based on a statistical model
MSM men who have sex with men
NAAT nucleic acid amplification tests, used during the DISCOVER study to detect gonorrhea and chlamydia from urine, rectal, and oropharyngeal swabs
NRTI nucleoside analog reverse transcriptase inhibitor, an HIV drug class
NS not significant
ODE emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®)
PBMC peripheral blood mononuclear cell, effector cells for HIV treatment efficacy
PCR polymerase chain reaction, a common laboratory technique used to make many copies of a particular region of deoxyribonucleic acid (DNA)
PEP postexposure prophylaxis, taking HIV drugs after potential exposure to HIV to prevent infection
PK pharmacokinetic(s), what the body does to a drug
PO oral administration
PrEP: pre-exposure prophylaxis, taking HIV drugs to reduce the risk of sexually acquired HIV
Q1: first quartile
Q3: third quartile
RBC: red blood cell
RBP: retinol binding protein, a measure used to assess kidney function
RNA: ribonucleic acid
RPV, R: rilpivirine
SAE: serious adverse event
SD: standard deviation, a statistical term describing how spread out values in a sample are from the mean
SHIV: simian HIV
SIV: simian immunodeficiency virus
SOC: system organ class, grouping of clinical and laboratory adverse events by body system, disease origin, or purpose
STB: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
STI: sexually transmitted infection
TAF: tenofovir alafenamide, a drug contained in Descovy (see also DVY)
TasP: treatment as prevention
TBLH: total body less head
TDF: tenofovir disoproxil fumarate, a drug contained in Truvada (see also TVD)
TFV: tenofovir, (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA), metabolic product of the prodrugs tenofovir disoproxil fumarate or tenofovir alafenamide (see also TDF and TAF)
TFV-DP: tenofovir diphosphate, active metabolite of tenofovir disoproxil fumarate and tenofovir alafenamide (see also TDF and TAF)
TGW: transgender woman, an individual whose assigned sex at birth was male but who identifies as female
TVD: emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®), a fixed-dose combination drug used in HIV treatment and prevention
UPCR: urine protein to creatinine ratio, a measure used to assess kidney function
US: United States
WHO: World Health Organization
1. BACKGROUND

Human immunodeficiency virus type 1 (HIV; HIV-1) infection is a global epidemic, with an estimated 1.1 million people in the United States (US) and 36.9 million people worldwide living with the condition {Centers for Disease Control and Prevention and Prevention 2019, UNAIDS 2017}. Although advancements in antiretroviral treatment have transformed HIV into a manageable chronic disease, there is still no cure for HIV, and maintaining suppression of the virus requires lifelong therapy {Department for Health and Human Services (DHHS) 2018}. The rate of new HIV infections has remained stable in the US since 2013, with approximately 39,000 people in the US receiving an HIV diagnosis each year. While the incidence of new infections has remained stable overall, it has increased in some groups, including young men ages 25 to 34 years who have sex with men (MSM) and individuals of African American race or Latinx ethnicity {Centers for Disease Control and Prevention 2019, National Center for HIV/AIDS Viral Hepatitis STD & TB Prevention: Division of HIV/AIDS Prevention 2019}. These statistics underscore the necessity for additional HIV prevention strategies in the US.

PrEP, or pre-exposure prophylaxis, is a biomedical HIV prevention strategy for individuals without HIV infection who are at risk of sexually acquired HIV. Truvada® (F/TDF) is a fixed-dose combination tablet of the nucleoside analog reverse transcriptase inhibitor (NRTI) emtricitabine (FTC; 200 mg) and the tenofovir (TFV) prodrug tenofovir disoproxil fumarate (TDF; 300 mg), which was first approved in the US in 2004 for use with other drugs for the treatment of HIV-1 infection, and later in 2012 for use in HIV PrEP in at-risk men and women {Gilead Sciences Inc. 2018, TRUVADA 2018a}. Truvada was subsequently approved in more than 50 countries for adults and in more than 30 countries for adolescents. Truvada (and generic versions) remains the only approved medication for PrEP worldwide, and guidelines from the Centers for Disease Control and Prevention (CDC), International AIDS Society (IAS)-USA, European AIDS Clinical Society (EACS), and multiple countries around the world recommend the use of Truvada for PrEP in individuals at risk of HIV infection {Center for Disease Control and Prevention (CDC) 2018a, Center for Disease Control and Prevention (CDC) 2018b, European AIDS Clinical Society (EACS) 2018, Saag 2018}. In 2017, the US Food and Drug Administration (FDA) approved an expansion of the adult PrEP indication to include adolescents weighing at least 35 kg.

Early studies demonstrated that the antiviral compound TFV administered to macaques prior to simian immunodeficiency virus (SIV) exposure prevented SIV infection, suggesting a possible use for antiviral medications in the prevention of HIV infection in humans at high risk {Tsai 1995}. Further nonclinical studies showed benefits of using a 2-drug combination for PrEP, rather than a single drug. First, the combination of FTC plus TDF was shown in several animal models to be more effective in HIV prevention compared with either agent alone {Denton 2008}. Second, oral administration of FTC plus TDF in macaques provided complete protection against an FTC-resistant virus containing the M184V mutation {Garcia-Lerma 2008}, an important factor in areas where drug-resistant viruses are frequently transmitted.

Daily oral Truvada is highly effective for PrEP when used as prescribed. This has been demonstrated in both clinical studies and in real-world use.
In iPrEx, an early Truvada for PrEP study in MSM, there was a 44% HIV risk reduction relative to placebo use, but adherence in this study was not high for the overall study population. Importantly, for the subset of iPrEx participants with a higher level of adherence and detectable drug levels, the HIV risk reduction was 92% \cite{Grant2010b, Grant2010c}.

Data from the Partners PrEP study in HIV serodiscordant heterosexual couples corroborated the iPrEx results. For the overall study population, there was a 75% HIV risk reduction while those with detectable levels of drug showed a 90% HIV risk reduction \cite{Baeten2012a}.

In each of the later PrEP studies IPERGAY and PROUD in MSM, which initiated more than a year after the publication and broad recognition of the correlation between adherence and efficacy, there was an 86% risk reduction observed in both studies \cite{McCormack2017, McCormack2015, Molina2015}.

In epidemiologic analyses of real-world use, increasing population-level uptake of PrEP has been independently associated with declining HIV incidence. There were no HIV infections reported in a Kaiser Permanente study, and very rare infections reported in various other PrEP projects. These include an Australian population PrEP implementation study in MSM, an aggregate Truvada demonstration project analysis, the IPERGAY study open-label extension, and others \cite{Grulich2018, Highleyman2018, Molina2017a, NewYorkCity2018, SanFrancisco2018, Sullivan2018, Tao2019, Volk2015}.

In a population-level analysis, among US jurisdictions with higher uptake of PrEP, the number of HIV diagnoses significantly declined, even when controlling for treatment as prevention (TasP)\footnote{Treatment as prevention (TasP) refers to the use of antiretroviral treatment to decrease the risk of HIV transmission} \cite{Sullivan2018}. In this analysis, there was a 4.7% annual reduction in new HIV infections per year in the quintile of US jurisdictions with the highest PrEP use from 2012 to 2016, even though only 11% of those with a CDC-defined PrEP indication were actually using PrEP. Moreover, in the quintile of US jurisdictions with the lowest PrEP use, there was a numerical increase of 1% to 2% per year in the number of HIV infections, and only 3% to 4% of those with a CDC-defined PrEP indication were using PrEP.

Based on clinical trial data and on literature reports, infections that are diagnosed while on Truvada for PrEP are usually due to an infection not diagnosed or detected at the start of the regimen, nonadherence to the regimen, or stopping the regimen entirely. Since the approval of Truvada for PrEP, and with several hundred thousand people around the world documented to have received at least 1 prescription for Truvada PrEP, there have been a total of only 6 HIV diagnoses reported with some clinical or laboratory confirmation of drug use \cite{Cohen2018, Colby2018, Hoornenborg2017, Knox2016, Markowitz2017, Thaden2018}. Resistance to either TFV or to FTC has been rarely reported, though genotypic evidence of transmitted drug resistance (to other drugs) is more common.

Even as Truvada for PrEP is highly effective in preventing HIV infection, its uptake across the US is relatively low. Despite the CDC estimate of at least 1.1 million individuals at risk of HIV

\footnotetext[1]{Treatment as prevention (TasP) refers to the use of antiretroviral treatment to decrease the risk of HIV transmission}
infection in the US {Smith 2018}, based on internal analyses of data compiled from the National Prescription Database, Gilead estimates that only 11.8% of those eligible for PrEP in the US (130,000 individuals, both male and female) were using Truvada for PrEP at the end of 2018. While uptake of and use of PrEP are not yet optimal in the US, Gilead and many national and local prevention service organizations continue to work to improve PrEP awareness, provide risk reduction education, reduce stigma, and increase engagement of at risk individuals without HIV infection in healthcare {Fauci 2019, Myers 2018}.

Surveys of healthcare providers and of current and lapsed PrEP users have shown that the established safety profile and the perceived risks associated with Truvada impact both the initial use of PrEP and persistence of use. While Truvada is generally well tolerated, safety data from chronic HIV treatment studies, from HIV prevention studies, and from real-world clinical experience show that the TDF component of Truvada is associated with bone and renal clinical events and with laboratory abnormalities, most likely off-target side effects caused by increased plasma TFV levels.

The TFV-related adverse effects are well characterized, as Truvada has been approved for chronic HIV treatment since 2004 and over 14 million person-years of exposure have accumulated {Gilead Sciences Inc. 2018, TRUVADA 2018b}.

Descovy® (F/TAF) is a fixed-dosed combination tablet containing FTC (200 mg), but Descovy incorporates a smaller dose of the novel TFV prodrug, TAF (25 mg). TAF is a distinct new molecular entity that is a phosphonamidite drug, making it more stable in plasma (the plasma TAF half-life is 75-times longer than that of TDF), so much less of it gets converted to TFV in plasma. This allows more TAF to enter peripheral blood mononuclear cells (PBMC), the effector cells for HIV treatment efficacy that are likely also key to HIV prevention efficacy {Anderson 2012c, Anderson 2012e, Baeten 2012}. This more efficient PBMC uptake of TAF over TDF results in a 90% decrease in plasma concentrations of TFV with Descovy, and favorable effects on bone and renal toxicity {Arribas 2017a, Gupta 2018, Hagins 2018, Raffi 2017, Ruane 2013}.

The pharmacokinetics of TAF also provided a rationale that Descovy would be effective for HIV prevention. The more efficient uptake (ie, more rapid, higher levels) of TAF into PBMCs means TAF can be transformed into higher intracellular levels of the active metabolite, TFV diphosphate (TFV-DP) {Custodio 2017, Schwartz 2018a}. A 25 mg dose of TAF has more antiviral potency than a 300 mg dose of TDF. TAF 25 mg resulted in a 1.5 log viral load reduction after 10 days of monotherapy (versus 1.0 log for TDF), and resulted in TFV-DP levels 4- to 7-fold higher than with TDF 300 mg in PBMCs {Ruane 2013}. The pharmacokinetic profile of TFV-DP in PBMCs with TAF may provide advantages for its use for PrEP as levels of TFV-DP in PBMCs considered therapeutic for protection against HIV infection (90% effective concentration [EC<sub>90</sub>] of 40 fmol/million cells<sup>2</sup>) are reached more quickly after the first dose (2 to

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<sup>2</sup> This threshold was estimated from the 16 fmol per million cell 90% effective concentration (EC<sub>90</sub>), derived from a case control analysis from the iPrEx study, using viably cryopreserved PBMCs. The 40 fmol per million cells is the estimate using freshly lysed PBMCs, which were used in DISCOVER and other studies. The EC<sub>90</sub> was commensurate with 2 to 3 doses per week on average. The estimated relative risk reduction for 4 or more doses per week on average was 96% (CI: 90%, > 99%).
3 hours for TAF vs 3 to 4 days for TDF) and remain above the therapeutic threshold longer after the last dose (16 days for TAF vs 9 to 10 days for TDF) compared with administration of TDF 300 mg (Gilead data). In addition, TFV-DP levels in PBMCs from individuals dosed at 33% (3 doses) of a weekly dosing schedule with TAF were 2-fold higher than TFV-DP in PBMCs from individuals dosed at 100% (7 doses) of a weekly dosing schedule with TDF {Yager 2019a}.

The pharmacokinetics of the components of Descovy (FTC and TAF) have been extensively characterized across 4 development programs for the treatment of HIV infection, Genvoya®, Descovy, Biktarvy®, and Odefsey®, each of which contain the same doses of FTC (200 mg) and TAF (25 mg).

Results of previous analyses demonstrate that the pharmacokinetics of FTC and TAF are not influenced by sex, age, race, or HIV infection status, allowing for extrapolation of clinical findings across populations living with and at risk of HIV {BIKTARVY® 2018a, BIKTARVY® 2018b, Custodio 2015, DESCOVY 2018, DESCOVY® 2017, Genvoya 2018b, GENVOYA® 2018b, Lutz 2018b}.

Descovy is already indicated, in combination with other antiretroviral agents, for the treatment of chronic HIV-1 infection in adults and pediatric patients. The initial approval in the US was in 2015, followed by subsequent approval in other regions {DESCOVY 2018, DESCOVY® 2017}.

Based on the improved pharmacokinetic profile, Descovy represents an advance over Truvada for use as PrEP, especially in cases where bone and renal safety are of particular concern {Cohen 2017, Mallipattu 2014, Pilkington 2018, Walsh 2009, Weaver 2016}. As compared with TDF-containing HIV treatment regimens, TAF-containing regimens have shown comparable or improved efficacy outcomes in clinical trials, even becoming statistically significant after nearly 3 years of follow-up in head-to-head comparison studies in treatment-naive individuals {Arribas 2017c, Mills 2015, Sax 2015, Stellbrink 2019, Wohl 2019}. Data from Gilead clinical trials and real-world use of TAF-containing products for HIV treatment exist for over 1.1 million people worldwide living with HIV, providing over 1.3 million person-years of exposure for TAF, and TAF has replaced TDF as part of the backbone of many treatment regimens for chronic HIV.

Since approval of the first marketed TAF-containing product Genvoya in 2015 {GENVOYA 2018a, GENVOYA® 2019}, HIV treatment guidelines have recommended use of TAF-containing regimens, and TAF-containing medicines are used internationally and considered the standard of care for the treatment of chronic HIV infection {Department for Health and Human Services (DHHS) 2018} {European AIDS Clinical Society (EACS) 2018}.

While TAF and TDF have comparable general safety outcomes, clinical TAF use has consistently shown better bone and renal safety outcomes in comparison with TDF.

Pooled data from 26 clinical trials in over 9000 people living with HIV showed no confirmed cases of proximal renal tubulopathy events with TAF, while there were 10 cases reported with TDF {Gupta 2019}. Second, renal-related drug discontinuations were also significantly more common with TDF than with TAF. Finally, those on TAF had significantly less change in serum creatinine and estimated glomerular filtration rate (eGFR) than in those on TDF.
From a bone perspective, TAF has a significantly more favorable bone safety profile than TDF in chronic HIV treatment studies {Wohl 2016}. TAF has significantly less impact on bone mineral density (BMD) and fewer high magnitude categorical changes in BMD. In the extension phases of the PrEP studies ATN-110 and ATN-113, men under 24 years old who were receiving a TDF-based regimen had blunted BMD growth, which did not improve 48 weeks after stopping TDF, suggesting that reductions in BMD that occur while on Truvada may not recover even after discontinuation of the drug {Havens 2019}.

The safety profile of FTC, the second NRTI contained in both Truvada and Descovy, is well established in chronic HIV treatment trials and in spontaneous reports from real-world use. The drug is extremely well tolerated with extremely rare drug-related side effects {EMTRIVA. 2018, EMTRIVA® 2018}.

Many PrEP users continue Truvada for PrEP for extended periods {Huang 2019}. As a result, the longer-term bone and renal safety benefits of Descovy for PrEP may be of greater importance. The bone safety advantage may be particularly meaningful for young adults and adolescents who are at high risk for HIV and who have not yet achieved peak bone mass (up to age 35). Both men and women over age 50, with increased risk of renal disease (related to age, diabetes, or hypertension) or with increased risk of bone disease (osteopenia, osteoporosis) may also meaningfully benefit from the use of a safer PrEP drug {Cohen 2017, Mallipattu 2014, Pilkington 2018, Walsh 2009, Weaver 2016}.

The renal safety profile of Descovy for PrEP, including in individuals with creatinine clearance as low as 30 mL/min, may also simplify the clinical management of PrEP with a reduced need for laboratory monitoring. In addition, in one short-term pharmacokinetic study of HIV prevention in women, a lower proportion of women taking Descovy reported gastrointestinal adverse events (AE) than those taking Truvada {Schwartz 2018b}; however, these observations have not been replicated elsewhere.

With both the pharmacokinetic benefits and the clinical trial data on the advantages of TAF in mind, Gilead designed the DISCOVER study to determine if Descovy for PrEP could confer the same benefits as Truvada for PrEP as have been seen for HIV treatment.

In addition to the existing chronic HIV treatment indication for Descovy {DESCOVY 2018, DESCOVY® 2017}, a second indication is being sought for Descovy use in PrEP to reduce the risk of sexually acquired HIV-1 in at risk adults and adolescents weighing at least 35 kg.

The indication proposed for Descovy use as PrEP is based in part on results from the DISCOVER study, in which 5387 adult men and transgender women (TGW) who have sex with men received Descovy or Truvada once-daily. Data from the DISCOVER study, when all participants had completed at least 48 weeks and 50% of participants had completed at least 96 weeks are presented for review. The key findings of this double-blind, randomized clinical Phase 3 trial clearly establish the noninferiority of Descovy to Truvada for PrEP, as well as the significant safety advantages for Descovy over Truvada. With 4369.7 person-years of follow-up for Descovy and 4386.2 person-years of follow-up for Truvada, DISCOVER confirms results from chronic HIV treatment studies that TAF is efficacious and has significant safety advantages over TDF, especially in bone and renal safety.
The indication in cis-women and adolescents is supported by extrapolation of DISCOVER data and data from previous clinical studies to these populations. Inclusion of women and adolescents in the proposed indication for Descovy for PrEP is based on bridging from the DISCOVER study data and from previous data from clinical studies of Descovy and F/TAF-containing products in healthy and in HIV-infected men, women, and adolescents. Clinical studies have consistently shown that exposure and clinical effects are consistent across populations, allowing for extrapolation strategy for results from DISCOVER study to at risk women and adolescents, who are often particularly vulnerable and disproportionally represented among newly HIV-infected persons.

The clinical data provided represent a considerable body of evidence on the safety and efficacy of Descovy for PrEP. Following approval, Descovy will clearly contribute to further reduce the spread of HIV in people who are at risk of HIV infection.
2. DESCOVY FOR PREP CLINICAL DEVELOPMENT PROGRAM

The initial evidence to support use of antiretroviral agents as HIV PrEP was derived from Gilead nonclinical studies of SIV/simian HIV (SHIV) transmission in macaques {Tsai 1995}. Early studies using subcutaneous injections of TFV showed that administration either before or shortly after oral, rectal, vaginal, or intravenous inoculation with SIV or SHIV prevented or delayed the onset of viremia {Garcia-Lerma 2009, Otten 2000, Van Rompay 1998, Van Rompay 2000, Van Rompay 2008, Van Rompay 2001}. These initial evaluations led to further studies on the timing and length of treatment, additional products (eg, F/TDF and F/TAF), administration routes, and study design refinements (eg, repeat-exposure model) to mimic high-risk human exposures and evaluate protection against multiple transmission events in each animal {Garcia-Lerma 2009}.

The successful protection against SIV and SHIV in these animal models also suggested that systemic exposure in PBMCs was the most likely and relevant correlate of protection against viral exposure through either rectal or vaginal routes. Further, the studies showed that the combination of oral administration of FTC and TDF offered complete protection against an FTC-resistant virus containing M184V in macaques, demonstrating that administration of both FTC and TDF is important in geographic areas with widespread access to antiretroviral drugs where drug-resistant viruses are frequently transmitted.

These nonclinical studies supported the development of TFV, alone and in combination with FTC in human clinical studies. Nonclinical studies are described in Appendix 9.3.

Details on the overall Descovy for PrEP clinical development program, including the design and conduct of the DISCOVER study, are provided in this section. Details on how the animal and clinical study results were used to bridge to use in cis-women and adolescent populations are provided in Section 5.

2.1. Overview of the Descovy for PrEP Clinical Development Program

The primary study supporting the efficacy and safety of Descovy for PrEP is the ongoing Phase 3 DISCOVER study evaluating the rate of HIV infection in adult cis-men and TGW who have sex with men and are at high risk of acquiring HIV infection (Table 1).

All participants in this ongoing study are receiving active drug, either daily Descovy or Truvada; there is no placebo group in the study.

Details of the DISCOVER study design are provided in Section 2.2. Results are presented in Sections 3 and 4. Data from the study demonstrates the efficacy and safety of Descovy for PrEP and provides clinical data in support of the significantly improved bone and renal safety profile of Descovy over Truvada.
The use of Descovy for PrEP in women and adolescents is supported by efficacy and pharmacokinetic data from the DISCOVER study, as well as by safety and pharmacokinetic data from previous studies in women and adolescents living with HIV and pharmacokinetic data from Phase 1 studies in healthy volunteers (Table 1). Background information and details on the extrapolation strategy used for Descovy for PrEP in women and adolescents are provided in Section 5.

Table 1. Overview of Key Data to Support Use of Descovy for PrEP

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Number of Participants by Treatment Regimen*</th>
<th>Data Presented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3 Clinical Study</td>
<td>Phase 3, ongoing, randomized, double-blind study to compare safety and efficacy of DVY versus TVD in HIV negative adult cis-men and TGW who have sex with men and are at risk of HIV infection.</td>
<td>DVY (N = 2694) TVD (N = 2693)</td>
<td>PK, efficacy, and safety</td>
</tr>
<tr>
<td>Extrapolation Reports</td>
<td>Efficacy of DVY for PrEP is extrapolated from cis-men and TGW to cis-women. Long-term safety of DVY in women living with HIV is extrapolated to cis-women at risk of HIV.</td>
<td>TAF-containing regimen (N = 429) TDF-containing regimen (N = 350)</td>
<td>PK, efficacy, and safety</td>
</tr>
<tr>
<td>Extrapolation Report for Adolescents</td>
<td>Efficacy of DVY for PrEP is extrapolated from adults to adolescents. Safety of DVY in adolescents living with HIV is extrapolated to adolescents at risk of HIV.</td>
<td>TAF-containing regimen (N = 50)</td>
<td>PK, efficacy, and safety</td>
</tr>
</tbody>
</table>

DVY = Descovy; PK = pharmacokinetics; PrEP = pre-exposure prophylaxis; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TGW = transgender women; TVD = Truvada
* N = number of people for whom safety data are presented

2.2. The DISCOVER Study

2.2.1. Study Design and Conduct

DISCOVER is an ongoing 96-week study conducted to determine the rate of HIV infection in cis-men (gender identity is the same as their assigned sex at birth) and TGW who have sex with men and are at high risk for acquiring HIV infection, who receive once-daily Descovy or Truvada. The objective of the study was to evaluate whether Descovy could be a safer and an equally or more effective alternative to Truvada for PrEP.

With increased recognition of the efficacy and availability of Truvada for PrEP, the design of clinical trials to test new PrEP regimens is challenging, as placebo-controlled PrEP trials are unethical, and the highly effective daily Truvada for PrEP standard of care must be used as an active comparator. The design and implementation of DISCOVER was discussed with prior PrEP investigators, with community members in North America and Europe, and with the FDA. Each provided valuable input during the planning stages.
The key study design elements, including sexual risk eligibility criteria, methods for HIV testing, the type and frequency of sexually transmitted infection (STI) testing, and other clinical assessments were based on previous studies of PrEP in MSM (eg, iPrEx, PROUD, IPERGAY). Due to the ethical considerations of using a placebo arm, the need to use an active-control group of Truvada for PrEP (already a proven and highly effective drug for PrEP) added to the complexities of DISCOVER study design. The protocol was submitted to FDA for review and recommendations from FDA were built into subsequent versions of the protocol. Gilead and the FDA mutually agreed on a double-blind, randomized controlled trial in approximately 5000 cis-men and TGW who have sex with men. The primary efficacy evaluation was a noninferiority comparison of the HIV incidence rate in the Descovy group as compared to the HIV incidence rate in the Truvada group, using an incidence rate ratio method {U. S. Department of Health & Human Services (DHHS) 2019, U.S. Department of Health and Human Services 2014}

The trial was conducted in accordance with Good Participatory Practice (GPP) {UNAIDS 2011} and Good Clinical Practice (GCP) guidelines, and, following suggestions from community members, Gilead established 3 separate community advisory boards to have ongoing discussions about trial conduct.

An independent data monitoring committee that was comprised of 2 academic PrEP experts, 1 academic PrEP statistician, and 1 community advocate was convened. This committee was asked to review unblinded data 3 times: once when 50% of participants had completed Week 24, once when 50% of participants had completed Week 48, and once when 50% of participants had completed Week 72. Based on the independent data monitoring committee (IDMC) reviews, no concerns were identified, and the group recommended that the study continue without changes.

DISCOVER study sites were chosen based on location in a community with high background HIV incidence and the ability to enroll individuals with significant sexual risk for HIV acquisition. Sites likely to have higher proportions of people of color and sites with knowledge and experience working with TGW were actively sought. Sites were also selected based on the ability for the investigator and study staff to meet all study requirements and conduct the study with high quality. Sites enrolling study participants reflected broad representation of medical facilities engaged in managing the HIV epidemic, and were located in diverse clinical settings, including private practices, hospital clinics, and STI clinics.

While some study sites were chosen based on having prior experience with PrEP (ie, PrEP clinical research and/or prescribing of PrEP), sites with an interest in PrEP but little or no clinical research experience were also included. Regardless of prior clinical research experience, all site staff involved in DISCOVER were licensed and qualified as applicable to their role, and trained on study-specific procedures. Sites ultimately determined to methods of recruitment necessary for their community, and each site determined who was screened for enrollment. Some sites used local community boards to assist them with recruitment and study conduct independent of Gilead.
During the study, sexual risk reduction was actively encouraged. Participants were educated at each visit about the increased risk of acquiring HIV infection through high-risk sexual behavior. Safer sex behavior was encouraged by site staff, and condoms and lubricant provided to participants at each site. Daily study drug adherence was also actively encouraged, with daily text messaging reminders available on an opt-in/opt-out basis. Sexually transmitted infection testing was performed at every visit to ensure that any STIs were promptly diagnosed and treated.

2.2.2. Study Population

Eligibility for DISCOVER was based on sexual risk of acquiring HIV infection. The study enrolled adult (at least 18 years of age) cis-men and TGW who have sex with men.

Eligible participants were required to have a negative HIV test at screening. Participants must have had at least 2 episodes of condomless anal sex (with at least 2 unique partners) in the 12 weeks prior to screening, or have had a diagnosis of rectal gonorrhea, rectal chlamydia, or syphilis in the 24 weeks prior to screening. The sexual behavior criteria used in the DISCOVER study were equally or more stringent than the criteria used by other PrEP studies in MSM {Grant 2010b, Grant 2010c, McCormack 2017} {McCormack 2015} {Molina 2015}. Sexual behavior criteria have also been used by the CDC to determine the number of individuals who should use PrEP due to their risk of HIV infection {Center for Disease Control and Prevention (CDC) 2017}.

Prior or current use of Truvada for PrEP by participants was allowed with no wash-out period required; participants were required to discontinue non-study drug PrEP medication before baseline.

2.2.3. Clinical Interventions

Study Drugs

The study drugs administered in DISCOVER were Descovy, a fixed-dose combination tablet of 200 mg FTC and 25 mg TAF, and Truvada, a fixed-dose combination tablet of 200 mg FTC and 300mg TDF. Each participant took 1 tablet containing active study drug and 1 placebo tablet, each once daily.

Study Visits

The DISCOVER study schema is shown in Figure 1.

Each participant had a screening visit no more than 30 days prior to enrollment to determine eligibility for randomization in the study. Each eligible participant was randomized to start active Descovy plus placebo to match Truvada, or active Truvada plus placebo to match Descovy at enrollment on Day 1.
Other than an on-site rapid HIV test, no venipuncture and no additional testing occurred at the baseline Day 1 visit. Follow-up visits occurred at Week 4 (1 month after baseline) and Week 12 (3 months after baseline), then every 12 weeks (3 months) thereafter. At each visit, blinded study medications were dispensed, and samples were collected for HIV testing as consistent with CDC guidelines (ref).

The DISCOVER study is currently ongoing, and each participant is to remain on blinded study drug until all participants complete at least 96 weeks of follow-up. Following this study milestone, all participants return on their usual 12 week visit schedule for their unblinding visit, and are informed of the active drug they had been taking. Open-label once-daily Descovy is offered to each participant at the unblinding visit for those who elect to continue. This open-label phase lasts for 48 weeks with the same follow-up visits every 12 weeks. Following the 48-week open-label Descovy period, the study will end. Study participants who complete the open-label phase and who reside in regions where Descovy is not yet approved and available for PrEP may continue to receive Descovy, with visits every 12 weeks, as locally allowed.

**Figure 1. DISCOVER: Study Schema**

* Participants continued blinded treatment until the last participant had reached Week 96, Gilead completed the Week 96 analysis, and the end of blinded treatment phase visit occurred.

**HIV Testing**

**Screening**

For detection of HIV infection at screening, on-site rapid testing on blood from a finger prick was conducted (fourth-generation antigen/antibody assay where locally approved, or third-generation antibody assay where fourth-generation assay not approved). Results of the on-site rapid test were available within 30 minutes. If the rapid test was positive, a retest was completed. Any screened participant with a confirmed positive rapid test was not enrolled. For each participant with a negative rapid test, a venous blood sample was collected for an additional HIV antigen/antibody test performed at the central laboratory. Any screened participant with a
positive central laboratory antigen/antibody test was not enrolled. Qualitative and quantitative HIV-1 RNA by polymerase chain reaction (PCR) testing was completed for any participant with a negative rapid test who showed symptoms of acute infection. Any screened participant diagnosed with HIV received counseling and was referred for appropriate care.

**Baseline**

For detection of HIV infection at baseline, on-site rapid testing was conducted using a locally approved assay. If the result for rapid testing was positive, a retest was completed. Any participant with a confirmed positive rapid test was not permitted to participate in the study. Qualitative and quantitative HIV-1 RNA by PCR testing was completed for any participant with a negative rapid test who showed symptoms of acute infection. Any participant diagnosed with HIV at baseline received counseling and was referred for appropriate care.

**Postbaseline**

The HIV testing algorithm for detection of HIV infection at each postbaseline visit is presented in Figure 2. At each postbaseline visit, HIV rapid testing was conducted using a locally approved assay. If the result for rapid testing was positive, a retest was completed. For each participant with a negative rapid test, a blood sample was collected for an additional HIV antigen/antibody test performed at the central laboratory. If the rapid retest result or the central laboratory test was positive, qualitative and quantitative HIV-1 RNA by PCR testing was completed (per CDC guidelines on HIV testing {Center for Disease Control and Prevention (CDC) 2018b}) and a sample was collected for possible genotypic resistance testing. Qualitative and quantitative HIV-1 RNA testing (central laboratory) was also required if significant risk exposure was reported, or if acute retroviral syndrome symptoms or signs were present. For study participants who had signs or symptoms of acute retroviral syndrome, or if a recent high-risk exposure was reported, the investigator was instructed to prescribe post-exposure prophylaxis (PEP) in accordance with CDC guidelines.
Figure 2. DISCOVER: HIV Testing Algorithm

At all study visits (except Screening and Day 1), the following algorithm* applies to the below evaluations:
1) Retest Rapid HIV-1 Ab/Ag test (at site)**
2) HIV-1 Ab/Ag test (at Central Lab), except at Day 1
3) Signs and symptoms consistent with acute infection
4) Participant had a recent exposure that the investigator considers high risk for HIV infection

Any Evaluation Positive

HIV-1 RNA tests***, including qualitative and quantitative tests (at Central Lab)

HIV-1 Infection Confirmed****

Stop Treatment

All Evaluations Negative

Continue Treatment in Study

---

* The HIV testing algorithm does not apply to HIV-infected participants.
** If the result for rapid testing is positive, a retest will be completed. If the retest rapid is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
*** May continue study drug, or may begin a full HIV treatment regimen until HIV-1 diagnosis is confirmed, at investigator discretion (Center for Disease Control and Prevention (CDC) 2018b).
**** HIV infection as 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), excluding HIV vaccinated participants, 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).

STI Testing

To ensure that any STIs were promptly diagnosed and treated, STI testing of 3 anatomical sites was conducted at every study visit. Nucleic acid amplification tests (NAAT) were used to analyze urine and the rectal and oropharyngeal swabs. The samples are being evaluated for gonorrhea and chlamydia, by either local laboratories in geographic proximity to investigative sites, or by a vendor contracted by Gilead (Covance Central Laboratory Services, Inc., Indianapolis, IN, USA). Syphilis testing was conducted at each visit according to local investigator preferences at local laboratories. Testing for any other STIs was performed as
needed per investigator discretion. All management of STIs (treatment and follow-up) was according to investigator practices. Sexually transmitted infection reporting to local public health agencies was required as determined by local requirements.

**Participant Questionnaire**

A confidential computer-assisted self-interview (CASI) questionnaire was used to collect data on sexual behavior and self-reported study drug adherence, and to provide opportunity to enroll to receive opt-in/opt-out text messaging reminders used to assist with adherence. The questionnaire was completed by participants on iPads at screening, baseline, and each study visit; site staff were not informed of the results. At each visit, participants were asked about types of sexual behavior, frequency of sexual encounters, number of unique sex partners, condom use, and recent study drug adherence.

Recreational drug and alcohol use history of DISCOVER participants was assessed at screening using the CASI questionnaire and Alcohol Use Disorders Identification Test (AUDIT) {Babor 2001}, respectively.

**General Safety Reporting and Management**

Adverse events described in this document are treatment emergent, 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 study drug discontinuation.

Laboratory abnormalities described in this document are also treatment-emergent. 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, or the last available date for participants who were still on study drug or on a study drug interruption at the time of analysis. If the relevant baseline laboratory data were missing, any laboratory abnormality of at least Grade 1 observed within the time frame specified above was considered treatment emergent.

Safety reporting and management of safety events in DISCOVER, including AEs and laboratory abnormalities, were conducted in a manner consistent with GCP and Gilead quality assurance standards. Instructions on safety reporting and management of safety events, including management of Grade 3 and Grade 4 AEs, serious AEs (SAEs), and laboratory abnormalities, were provided in the study protocol, and site staff were trained on management of safety events. Adverse events were reported on electronic case report forms at every visit, whether the visit was scheduled or unscheduled. Mandatory drug interruptions were required for some more severe drug-related safety events and are described in detail in the study protocol.

Serious AEs were reported expeditiously to regulatory agencies in accordance with established guidelines. Safety laboratory parameters were evaluated at each visit, with samples sent to a central laboratory for processing. Investigator signatures were required to certify that all required safety laboratory assessments were completed. Accelerated follow-up was required for all
Grade 3 and Grade 4 clinically relevant (as determined by the investigator) safety laboratory abnormalities

**Bone Safety**

To evaluate bone safety in TAF versus TDF, dual-energy x-ray absorptiometry (DXA) scanning was performed on a subset of participants at sites with access to DXA scanning. A subset of nearly 400 participants was enrolled in this BMD study, a sample size based on the expected BMD loss from prior TAF vs. TDF clinical studies. Bone mineral density was evaluated at baseline and every 48 weeks. All DXA scanners were standardized and all data were centrally read and interpreted using standardized processes by a Gilead-contracted vendor (Bioclinica, Doylestown, PA, USA). The results and interpretation were provided to investigators and participants in real time. Use of bisphosphonates, calcium, and vitamin D was allowed as needed.

**Renal Safety**

**Glomerular Function**

Serum creatinine was used to calculate eGFR using the Cockcroft-Gault formula (eGFR$_{CG}$) for creatinine clearance \{Cockcroft 1976\}. Glomerular function was also assessed by urine protein to creatinine ratio (UPCR).

**Renal Tubular Function**

Proximal tubular dysfunction was assessed by the ability of the kidney to filter and reabsorb the 2 low molecular weight proteins, beta-2-microglobulin and retinol binding protein (RBP), both of which are freely filtered through the glomeruli of a healthy kidney and reabsorbed by the proximal tubules. The ratio of RBP to creatinine and the ratio of urine beta-2-microglobulin to creatinine were determined. In proximal tubular dysfunction, beta-2-microglobulin and RBP are not reabsorbed and the tubular marker ratios increase.

**Pharmacokinetic Assessments**

Trough pharmacokinetic blood and PBMC samples were drawn at Week 4 to determine the pharmacokinetic profile of intracellular TFV-DP and FTC-TP, and plasma TFV and FTC in a randomly preselected subset of 10% of participants.

Knowledge of an established pharmacokinetic-pharmacodynamic relationship and HIV incidence in the prior Truvada for PrEP trial, iPrEx was used to estimate a therapeutic threshold based on TFV-DP concentrations measured in cryopreserved PBMCs from participants in iPrEx. Briefly, an exponential regression model of TFV-DP concentrations demonstrated that a TFV-DP concentration of 16 fmol per million cells was associated with 90% HIV risk reduction relative to placebo \{Anderson 2012d\}. This threshold of HIV risk reduction corresponds to 40 fmol per million cells in freshly lysed PBMCs \{Anderson 2012e\}, the method of processing that was used to evaluate TFV-DP concentrations in PBMCs in the DISCOVER study.
2.2.4. Adherence Assessments

Adherence to study drug was measured using both subjective means (self-report and pill counts) and an objective measure (TFV-DP levels in red blood cells [RBC] from dried blood spot samples [DBS testing] {Anderson 2012c, Anderson 2018, Castillo-Mancilla 2013, Grant 2014a, Yager 2019b}).

For self-reported adherence, each participant was asked in the CASI questionnaire at each visit how many study drug doses they had missed since the previous visit. To determine adherence by pill counts, study drug bottles were returned at each visit and used to count the number of pills not taken since the last visit.

Measurement of TFV-DP levels in RBC using DBS is a validated method of assessing TFV-DP levels that represents cumulative/averaged study drug adherence over the preceding 8 weeks prior to collection of the DBS sample. DBS testing is more indicative of longer-term adherence than plasma testing of drug levels, as plasma levels reflect only the most recent dose taken.

Adherence was estimated for the study population using a randomly selected subset (approximately 10%) of the study population by measuring TFV-DP and FTC-TP in RBCs using DBS samples. DBS samples were collected in all participants at each visit, and testing was conducted on samples from the visit of diagnosis and all prior visits for each participant diagnosed with HIV. One 3-mm punched disk was used for quantitation of TFV-DP from Truvada, and two 7-mm punched disks were used for quantitation of TFV-DP from Descovy. TFV-DP in RBCs was lower for Descovy compared with Truvada, thus more RBCs (and bigger punches) were needed to provide estimated gradients of adherence for Descovy similar to those established for Truvada. The levels of the active metabolite TFV-DP measured by DBS testing were associated with the number of doses of each study drug taken in 1 week as follows:

<table>
<thead>
<tr>
<th>Adherence Level (Daily Tablets/Week)</th>
<th>Low (&lt;2)</th>
<th>Medium (2-3)</th>
<th>High (≥4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/TDF (fmol/Punch)</td>
<td>&lt; 350</td>
<td>350 to &lt; 700</td>
<td>≥ 700</td>
</tr>
<tr>
<td>F/TAF (fmol/Punches)</td>
<td>&lt; 450</td>
<td>450 to &lt; 900</td>
<td>≥ 900</td>
</tr>
</tbody>
</table>

For Truvada, dosing of at least 4 doses per week on average was associated with high (96% to 100%) HIV prevention {Grant 2014b, Grant 2010c}. The number of Descovy doses required per week for HIV prevention has not yet been defined. Further details are provided in Appendix 9.1.

In a prespecified case-control analysis, levels of TFV-DP in DBS samples from participants who became infected with HIV during the study ("cases") were compared with TFV-DP levels measured in DBS from randomly selected participants who did not become infected with HIV ("controls"). For each case participant who was infected with HIV, 5 control participants without HIV were matched based on the treatment group, geography (in the following order of preference: site, city, state), timing of the HIV diagnosis in the case participant, and on the presence or absence of a rectal STI on or prior to the HIV diagnosis. In both the case and control
participants, concentrations of study drug in plasma (ie, TFV and FTC) and levels of TFV-DP and FTC-TP in DBS were evaluated in samples taken at the visit of HIV diagnosis and at all study visits prior to the HIV diagnosis in the case participant.

2.2.5. Statistical Analysis and Considerations

Since DISCOVER required the use of an active control arm, the statistical methods required for the analysis of the primary efficacy endpoint analysis had not been used previously in a randomized clinical study of HIV prevention. As participants in both arms in DISCOVER received active drug during the study, evaluation of the noninferiority of Descovy compared with Truvada was considered appropriate.

The primary efficacy endpoint was the HIV incidence rate per 100 person-years in the study. Per FDA agreement, the efficacy analysis was time-driven (not event driven) and was conducted once all study participants completed 48 weeks and half of participants had completed 96 weeks.

For the primary efficacy analysis, the incidence rate ratio was calculated by dividing the HIV incidence rate (number of participants who became infected per 100 person-years of follow-up in the study) in the Descovy group by the HIV incidence rate in the Truvada group at a prespecified time point when all participants had 48 weeks of follow-up and at least 50% of participants had 96 weeks of follow-up after randomization.

The primary efficacy endpoint analysis was time-driven and not based on the number of HIV infection events reported. This followed FDA guidance on the development of vaginal microbicides for the prevention of HIV infection, and is consistent with FDA draft guidance on developing systemic drug products for PrEP {U. S. Department of Health & Human Services (DHHS) 2019, U.S. Department of Health and Human Services 2014}.

Prior Truvada for PrEP studies that enrolled populations similar to that planned for DISCOVER, were used to determine the effect size and the sample size required for the noninferiority analysis. Based on equal weighting of incidence rates from the prior Truvada for PrEP studies, iPrEx³, PROUD, and IPERGAY {Grant 2010a, McCormack 2015, McCormack 2017, Molina 2015}, an HIV infection rate of 1.44 infections per 100 person-years was calculated for participants taking Truvada and used as the expected rate for each group in DISCOVER. (iPrEx was larger than the other 2 studies, but also had lower study drug adherence, and was therefore considered of the same weight as the more recent PROUD and IPERGAY studies, which started enrollment after Truvada was approved for PrEP and had higher study drug adherence.) The observed HIV incidence in the pooled placebo arm of these 3 studies was 6.96 infections per 100 person-years. The noninferiority margin was selected to preserve 50% of Truvada effect versus placebo. A noninferiority margin of 1.62 that was calculated based on previous Truvada for PrEP studies is the square root of the lower bound of the 95% confidence interval (CI) (2.64) of the rate ratio comparing placebo over Truvada. A sample size of 5000 participants (2500 participants in each group with 1:1 randomization), an average of 2 years of follow-up (ie, 50% of participants would have a minimum of 2 years of follow-up), and an HIV infection rate

³ The URAI (unprotected receptive anal intercourse) subset within the study
of 1.44 infections per 100 person-years in each of the 2 arms provided at least 82% power to show that Descovy is noninferior to Truvada for use as PrEP.

Key secondary safety endpoints in DISCOVER were 2 bone density endpoints, 2 proximal tubular protein endpoints, UPCR, and serum creatinine. These were chosen based on observations from chronic HIV treatment studies of TAF- versus TDF-containing medicines, and were assessed in a sequential analysis cascade (from most to least likely to show statistical significance between arms) that required significance of the earlier endpoints before the later endpoints could be evaluated for significance.

The 6 key secondary safety endpoints were tested in the following sequential order using the fallback procedure {Wiens 2005} with prespecified 2-sided alpha levels:

- Percentage change from baseline in hip BMD at Week 48 in subset of participants (alpha spent = 0.02)
- Percentage change from baseline in spine BMD at Week 48 in subset of participants (alpha spent = 0.01)
- Percentage change from baseline in urine beta-2-microglobulin to creatinine ratio at Week 48 (alpha spent = 0.02)
- Percentage change from baseline in urine RBP to creatinine ratio at Week 48 (alpha spent = 0.00)
- Distribution of urine protein and UPCR categories at Week 48 (alpha spent = 0.00)
- Change from baseline in serum creatinine at Week 48 (alpha spent = 0.00)

In the primary efficacy analysis, alpha penalties were incorporated to take into account the 3 unblinded analyses at the IDMC data cuts. Independent data monitoring committee data cuts occurred when 50% of participants had passed Week 24, when 50% of participants had passed Week 48, and when 50% of participants had passed Week 72. For each independent data monitoring committee data cut, the alpha penalty was 0.00001; therefore, the alpha level for the primary efficacy endpoint was adjusted to 0.04997 corresponding to a cumulative CI of 95.003%.
3. DISCOVER EFFICACY RESULTS

3.1. DISCOVER Primary Efficacy Analysis

Screening for DISCOVER began in September 2016 in the US, with sites in Canada and Europe initiating later, and enrollment was completed in May 2017. Participants were enrolled in 94 sites across 11 countries in the US, Canada, and Europe.

Disposition of all participants screened for the DISCOVER study is presented in Figure 3. Five thousand three hundred and eighty-seven participants were randomized and enrolled into the DISCOVER study, and received at least 1 dose of study drug, with 2694 in the Descovy group and 2693 in the Truvada group. As of the primary analysis data cut date, 83% to 84% of participants remained active on study drug.

The majority of participants who prematurely discontinued from the study were lost to follow-up or discontinued due to participant decision. The most frequent reasons for participant decision to discontinue prematurely from the study were as follows: withdrew consent, moved, in a monogamous relationship, reduced sexual risk, and work, school, or military obligations. Only 1.3% to 1.7% of study participants discontinued study drug due to an adverse safety event.
Figure 3. DISCOVER: Participant Disposition

Met All Eligibility Criteria and Not Randomized* (N = 94)

Randomized (N = 5399)

Screened (N = 5857)

Screen Failures Who Were Not Randomized (N = 364)

HIV Positive at Screening (N = 49)

F/TAF Randomized (N = 2700)

F/TAF Randomized and Treated (N = 2694)

Still on Randomized Study Drug (N = 2242)

Prematurely Discontinued from Randomized Study Drug (N = 452)
- Lost to Follow-up (n=201)
- Participant Decision (n=193)
- Adverse Event (n=36)
- Non-compliance with Study Drug (n=8)
- Investigator’s Discretion (n=5)
- HIV-1 Infection (n=4)
- Protocol Violation (n=4)
- Death (n=1)

F/TAF Randomized and Not Treated^ (N = 6)

F/TDF Randomized (N = 2699)

F/TDF Randomized and Treated (N = 2693)

Still on Randomized Study Drug (N = 2263)

Prematurely Discontinued from Randomized Study Drug (N = 430)
- Participant Decision (n=175)
- Lost to Follow-up (n=170)
- Adverse Event (n=59)
- Non-compliance with Study Drug (n=12)
- Investigator’s Discretion (n=10)
- HIV-1 Infection (n=9)
- Protocol Violation (n=3)
- Death (n=2)

* Among 94 participants who met all eligibility criteria and were not randomized, the reasons (N) were: lost to follow-up (32); withdrew consent (51); investigator’s discretion (3); outside of visit window (6); enrollment closed (1); participant death (1).

^ Among 12 participants randomized but never dosed, the reasons (N) were: protocol violation (1), withdrew consent (8), HIV-1 infection (2), investigator’s discretion (1).
3.1.1. Demographics and HIV Risk Characteristics

Demographics were similar across the groups.

The median age of the study population was 34 years. By age category, 11.7% were 18 to < 25 years, 75.0% were ≥ 25 to < 50 years, and 13.3% were ≥ 50 years. Most participants were cis-men (5313 participants [98.6%]); 74 (1.4%) self-identified as TGW.

Most participants were white (4511 participants, 83.9%); with 474 (8.8%) of participants reporting black or mixed black race, and 233 (4.3%) reporting Asian race. Within the US, approximately 12.8% of participants reported black or mixed black race, which is similar to the proportion of those in the US population overall who are of black or African American race (13.4% as of July 2018) and higher than the estimated proportion of the US male lesbian, gay, bisexual, and transgender (LGBT) population who are of black race (10%) {The Williams Institute UCLA School of Law 2019} {United States Census Bureau 2018}. Approximately one-quarter (1318; 24.5%) of participants were of Hispanic or Latinx ethnicity, which is also higher than the estimated 23% of the US male LGBT population who are Latinx.

All study participants were eligible for participation in DISCOVER based on a negative HIV test at screening and on the basis of sexual risk; 49 new HIV diagnoses were reported at the screening visit. The level of self-reported sexual risk behavior was high and above the level required for study eligibility, with a mean of 4 condomless anal sex partners in the 90 days prior to screening across the study population. The majority of participants (61.3%) reported 2 or more episodes of condomless receptive anal sex with 2 or more unique partners.

Medical history of STIs prior to screening was also indicative of a study population at high risk for sexually acquired HIV infection. The proportions of participants with rectal gonorrhea, rectal chlamydia, or syphilis in the 24 weeks prior to screening were 9.9%, 12.5%, and 9.2%, respectively.

At baseline, 905 participants (16.8%) were using Truvada for PrEP, and 1247 participants (23.1%) had previously used Truvada for PrEP. Use of at least one 4-week HIV PEP regimen in the 12 months prior to screening was reported by 15.6% of participants overall, and 5.0% of participants reported having used 2 or more such regimens during the same period. The majority of participants (61.4%) reported that they did not use a condom frequently, and the majority of participants (74.1%) did not ask their partner to use a condom for anal sex to manage the risk of getting HIV.

Two-thirds of participants (66.7%) reported use of recreational drugs (many as part of chemsex) in the 3 months prior to screening. Most participants (91.2%) reported that they ever used alcohol. The mean (standard deviation [SD]) AUDIT score was 5 (3.6); most participants (82.7%) had an AUDIT score less than 8, indicating that they were likely not engaging in harmful or hazardous drinking or at risk of alcohol dependence, although 22.8% of participants reported they had engaged in binge drinking, defined as 6 or more drinks on 1 occasion at least monthly (AUDIT question 3). Most participants (82.8%) had not had a feeling of guilt or remorse after drinking (often correlated with alcoholism) during the past year (AUDIT question 7).
3.1.2. Overall Adherence to Study Drug

Adherence to study drug was high as evaluated using both subjective and objective means.

Adherence assessed by pill counts of unused study drug in bottles returned at each visit showed median (Q1, Q3) adherence of 97.9% (93.4%, 99.8%) in those taking Descovy and 98.0% (93.5%, 99.9%) in those taking Truvada over the duration of the study.

Self-reported adherence was high, with a median adherence rate of 100% in both treatment groups.

Using TFV-DP levels measured in RBCs, adherence to study drug for the overall study population in the randomly preselected subset (n = 536) was found to be high in both groups throughout the study, as displayed in Figure 4. Most participants had levels of TFV-DP in RBC from DBS consistent with study drug dosing with at least 4 tablets per week on average, the Truvada dosing requirement associated with >90% reduction in HIV incidence.

**Figure 4.** DISCOVER: TFV-DP Concentrations in Red Blood Cells from Dried Blood Spot Samples for Descovy (fmol/punches) and Truvada (fmol/punch)

Boxes represent interquartile range, whiskers represent 1–99% percentile, and black circles represent outliers. Values > 4500 are not displayed.

3.1.3. Primary Efficacy Endpoint and Assessment of Noninferiority of Descovy to Truvada

Analysis of the prespecified primary efficacy endpoint showed that Descovy was noninferior to Truvada for use in PrEP.
A total of 22 HIV infections were diagnosed during the study in 8756 person-years of follow-up, as follows: 7 in the Descovy group (incidence rate = 0.16 infections per 100 person-years), and 15 in the Truvada group (incidence rate = 0.34 infections per 100 person-years) (Figure 5). The incidence rate ratio (Descovy over Truvada) was 0.47, with a 95.003% CI of 0.19 to 1.15. The upper bound of the 2-sided 95.003% CI for the incidence rate ratio was less than the prespecified noninferiority margin of 1.62; therefore, Descovy was demonstrated to be noninferior to Truvada at preventing HIV infection. This incidence rate ratio of 0.47 represents a 53% numerical reduction in HIV incidence for Descovy over Truvada, the current standard of care.
Figure 5. DISCOVER: HIV Incidence and Incidence Rate Ratio at the Primary Efficacy Endpoint

**HIV Incidence**

- **F/TAF**
  - 7 infections
  - 4370 PY
  - n=2694

- **F/TDF**
  - 15 infections
  - 4386 PY
  - n=2693

**Incidence Rate Ratio (95% CI)**

- Favors F/TAF
  - 0.16
  - 0.19

- Favors F/TDF
  - 0.34
  - Noninferiority

RR = 1, no difference
NI margin

1.15
1.62
2
Sensitivity Analysis of the Primary Efficacy Endpoint Excluding Baseline Infections

Assessment of TFV-DP in RBCs using DBS testing provides a validated method to evaluate drug adherence data over the approximately 8 weeks before sample collection. Seventeen of the 22 HIV diagnoses were due to infections that occurred on study. Of these 17 HIV diagnoses, 15 participants had TFV-DP levels by DBS testing that were very low or undetectable (5 in the Descovy group and 10 in the Truvada group) at the visit of HIV diagnosis. One participant in the Descovy group had low to medium levels of TFV-DP corresponding to taking 2 to 3 doses per week, and 1 participant in the Truvada group had high levels of TFV-DP corresponding to taking 4 or more doses per week. The high levels of TFV-DP measured for the participant in the Truvada group had been imputed from TFV-DP levels in a sample from the visit prior to the HIV diagnosis visit, as this participant was missing DBS data at the diagnosis visit.

A blinded review of data from the 22 participants who were diagnosed with HIV demonstrated that 5 participants were likely to have been infected before starting study drug\(^4\). Each of these 5 participants was diagnosed in the first several weeks of the study, each reported sexual behavior consistent with a possible HIV exposure around the time of study entry, each reported good study drug adherence and had higher levels of detectable study drug, and 4 of the 5 had genotypic resistance to FTC. Of the 5 suspected baseline infections, 1 occurred in the Descovy group and 4 occurred in the Truvada group. While all study participants had both a rapid on-site HIV test and a second venous blood sample sent to the central laboratory for HIV testing at the screening visit, only a rapid on-site HIV test was conducted at the baseline visit. As fourth-generation HIV-1 antigen/antibody rapid on-site testing was not universally available at all sites at the beginning of the DISCOVER study, a third-generation HIV-1 antibody rapid on-site test was used. The third-generation HIV-1 antibody rapid on-site test is less sensitive than the fourth-generation HIV-1 antigen/antibody rapid on-site test and may have failed to detect the new HIV diagnosis in the 5 individuals with suspected baseline infection.

As a sensitivity analysis, noninferiority by the incidence rate ratio was assessed excluding the 5 participants with early HIV diagnoses. Excluding these participants from the analysis leaves 6 participants in the Descovy group (incidence rate = 0.14 infections per 100 person-years of follow-up), and 11 participants in the Truvada group (incidence rate = 0.25 infections per 100 person-years of follow-up) with HIV infection. The incidence rate ratio was 0.55, with a 95.003% CI of 0.20 to 1.48, confirming the noninferiority established in the primary endpoint analysis.

Bayesian Analysis of the Primary Efficacy Endpoint

To contextualize the results of the primary efficacy endpoint, a post-hoc Bayesian analysis using a noninformative, Jeffreys, prior distribution was performed. Details for this analysis method are provided in Appendix 9.2.

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\(^4\) As determined through blinded, independently conducted medical review of HIV infection cases by 3 physicians, who considered the timing of the diagnosis, the first available viral load data, pharmacokinetic data, subjective reports of adherence, genotyping data, and confidentially provided possible HIV exposure information.
The Bayesian analysis shows that the posterior probability that Descovy is more effective than Truvada (rate ratio of HIV incidence < 1) is 95.6% while the posterior probability that Descovy is noninferior to Truvada (rate ratio of HIV incidence < 1.62) is 99.8% with the predicted median of HIV incidence rate ratio of 0.47, and 95% credible interval (0.18, 1.11). The Bayesian analysis results are consistent with, and support, the results obtained by the primary analysis method (parametric Poisson regression).

3.1.4. Efficacy in Subgroups

The numbers of participants with HIV infection in prespecified\(^5\) subgroups based on demographics and baseline characteristics are presented by treatment group in Figure 6.

The overall HIV incidence rates were 0.16 and 0.34 for the Descovy and Truvada groups, respectively. Notably, there were no significant differences in HIV incidence rates between the Descovy and Truvada groups, no significant differences between the subgroups, and no significant differences between subgroups and the overall population.

Figure 6. DISCOVER: HIV Incidence Rate Ratios in Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Descovy</th>
<th>Truvada</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.16(0.1, 0.3)</td>
<td>0.34(0.2, 0.5)</td>
<td>0.47 (0.19, 1.15)</td>
</tr>
<tr>
<td>Age &lt;25 y</td>
<td>0.82(0.2, 2.1)</td>
<td>0.66(0.1, 1.8)</td>
<td></td>
</tr>
<tr>
<td>Age ≥25 y</td>
<td>0.08(0.1, 1.6)</td>
<td>0.31(0.2, 0.6)</td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td>0.27(0.2, 2.4)</td>
<td>0.82(0.2, 2.4)</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>0.08(0.2, 0.3)</td>
<td>0.46(0.2, 0.8)</td>
<td></td>
</tr>
<tr>
<td>Ex-US</td>
<td>0.28(0.1, 0.7)</td>
<td>0.18(0.2, 0.8)</td>
<td></td>
</tr>
<tr>
<td>BL TVD for PrEP</td>
<td>0.0(0, 0.5)</td>
<td>0.14(0, 0.5)</td>
<td></td>
</tr>
<tr>
<td>Recreational drug use</td>
<td>0.21(0, 0.5)</td>
<td>0.33(0, 0.5)</td>
<td></td>
</tr>
<tr>
<td>Binge alcohol use</td>
<td>0.08(0, 0.5)</td>
<td>0.29(0, 0.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;3 URAI partners</td>
<td>0.10(0, 0.5)</td>
<td>0.26(0, 0.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;3 URAI partners</td>
<td>0.33(0, 1.3)</td>
<td>0.64(0, 1.3)</td>
<td></td>
</tr>
</tbody>
</table>

3.1.5. Adherence to Study Drug Correlates with Efficacy

Using DBS testing of TFV-DP levels in RBCs provides an objective measure of study drug adherence in the 8 weeks prior to sample collection. The high efficacy observed with Descovy and Truvada in DISCOVER compared with prior PrEP studies was driven by a high rate of

\(^5\) DISCOVER study statistical analysis plan.
adherence to study drug based on TFV-DP levels in RBCs; most HIV infections occurred in participants who were not taking study drug.

By DBS testing, participants who became infected with HIV had lower levels of TFV-DP than participants who remained uninfected. The median level of TFV-DP at the visit of HIV diagnosis in the Descovy group was 277 fmol per punches in the 7 participants diagnosed with HIV infection (cases) compared with 1736 fmol per punches in the matched uninfected participants (controls). In the Truvada group, the median level of TFV-DP at the visit of HIV diagnosis was 133 fmol per punch in the 15 participants diagnosed with HIV infection (cases) and 1075 fmol per punch in the matched uninfected participants (controls). The differences between infected case participants and matched uninfected control participants in both groups were highly statistically significant (Descovy, p = 0.001; Truvada, p < 0.001).

Participants in both groups who were infected with HIV had a median TFV-DP level associated with taking 2 or fewer tablets per week at the time of HIV infection diagnosis, while the matched uninfected control participants had higher median TFV-DP levels at each visit, associated with taking at least 4 tablets per week Figure 7. Median TFV-DP levels in the matched uninfected control participants were similar to those estimated for the overall study population (Section 3.1.2).

Figure 7. DISCOVER: TFV-DP Concentrations in Red Blood Cells from Dried Blood Spot Samples in Cases and Matched Controls for Descovy (fmol/punches) and Truvada (fmol/punch)

Boxes show median (Q1, Q3); whiskers show 5% and 95% percentiles; black circles show outliers. Values > 4000 not displayed.
With high adherence to study drug (versus medium or low adherence) by DBS testing, the odds ratios associated with risk of HIV in DISCOVER were 0.05 (95% CI: < 0.001, 0.40) with Descovy and 0.15 (95% CI: 0.03, 0.55) with Truvada.

3.1.6. Pharmacokinetic Efficacy Effects of TAF

In DISCOVER, there was less than half the number HIV infections in the Descovy group compared with the Truvada group, even though HIV risk factors were similar across the 2 groups and adherence by both the subjective measures and by the DBS testing of TFV-DP levels was comparable.

In the same 10% of participants from whom DBS samples were evaluated, trough TFV, TFV-DP, FTC, and FTC-TP were measured in plasma and PBMCs at Week 4, and FTC was measured in plasma every 12 weeks, and there were clear differences in PBMC exposures of active study drug. In the DISCOVER study at Week 4, it was estimated for the overall study population that 98% of participants in the Descovy group, but only 68% of participants in the Truvada group had TFV-DP levels in PBMCs above the 40 fmol per million cells threshold (Gilead data and {Anderson 2012b}). These data provide a plausible explanation for the difference in the number of HIV infections between the Descovy and Truvada groups.

3.1.7. Virology Resistance Analyses

Of the 22 participants infected with HIV, 19 participants had a satisfactory sample for amplification for genotypic resistance testing. Only 4 samples tested showed evidence of genotypic resistance to study drug (all from participants in the Truvada group). All were M184 mutations, conferring resistance to FTC, and each participant was suspected to have acquired infection before baseline or before levels of study drug considered efficacious had been reached. Several infected participants also had known transmitted drug resistance mutations suggesting that the resistance may have been pre-existing. No participant in the Descovy group had resistance, and no participant had resistance to TFV.

3.1.8. Context for the Efficacy Observed in DISCOVER

Compared with efficacy outcomes with Truvada in MSM in earlier PrEP studies (eg, iPrEx, PROUD, IPERGAY), Descovy and Truvada each had a higher rate of efficacy in DISCOVER, as measured by the HIV incidence rates in both groups {Grant 2010a, Grant 2010c, Hare 2019, McCormack 2015, Molina 2015}. The HIV incidence rates in DISCOVER are among the lowest ever reported in a randomized clinical trial of HIV prevention.

In the absence of a placebo group as used in previous studies of PrEP, context for the efficacy results in DISCOVER is provided by calculations of background HIV incidence rates had participants not been taking Descovy or Truvada for PrEP. In the first indirect analysis, the rectal gonorrhea and HIV incidence rates in DISCOVER were compared to rectal gonorrhea rates correlated with HIV infection rates in a recently published cohort of studies {Mullick 2019}. Using this method, the high rectal gonorrhea rates observed in DISCOVER (21.6 infections per 100 person-years for Descovy and 20.5 infections per 100 person-years for Truvada) predicted the HIV incidence rates, had participants not been taking PrEP, to be 6.61 infections per
100 person-years for Descovy (95% prediction interval: 3.92, 9.29) and 6.36 infections per 100 person-years for Truvada (95% prediction interval: 3.69, 9.03). These predicted HIV incidence rates correspond with risk reductions of 98% for Descovy and 95% for Truvada compared with no PrEP use. While this comparison is limited in that data from historical studies are used, these higher rectal gonorrhea rate-predicted HIV infection rates compared with the actual HIV incidence rates observed in DISCOVER support the effectiveness of both Descovy and Truvada for preventing HIV infection.

In the second indirect analysis providing further context for the efficacy results in the study, a background rate of HIV transmission was calculated for geographical areas where US DISCOVER sites were located. The HIV incidence rates in the DISCOVER study population were compared with the HIV infection rate in a population of MSM not taking PrEP and not part of DISCOVER who were located within the metropolitan statistical areas (MSAs) where DISCOVER sites were located. Analyses of epidemiological data showed that in 25 US MSAs overlapping with DISCOVER sites, the 2016 HIV infection rate was 4.02 infections per 100 person-years of follow-up (95% CI: 3.96, 4.09) in non-DISCOVER men not taking PrEP who have sex with men \{Hare 2019, Mera 2019\}. The HIV incidence rates in US DISCOVER study participants were 0.08 infections per 100 person-years of follow-up (95% exact CI: 0.01, 0.28) in the Descovy group and 0.45 infections per 100 person-years of follow-up (95% exact CI: 0.23, 0.78) in the Truvada group. These predicted HIV incidence rates correspond with risk reductions of 98% for Descovy and 89% for Truvada compared with no PrEP use. Although the HIV infection rate used in the comparison is based on data collected through surveys and local population sampling rather than as part of a formal clinical study, the significantly higher infection rate for individuals outside of the DISCOVER study is a useful indicator that the study was conducted in areas of high HIV transmission, thus demonstrating that both Truvada and Descovy are effective in preventing HIV infection.

A direct contextual comparison may be made by calculating the background HIV incidence rate for the DISCOVER study. Using the 5 suspected baseline infections, an incidence rate of 2.09 infections per 100 person-years (95% CI: 0.68, 4.87) was calculated over 239.5 person-years of follow-up (the time from the screening visit to the first dose for all participants in the full analysis set \[N = 5387\]). Although this approach is conservative and likely to underestimate the background placebo rate in DISCOVER, the placebo HIV incidence rate calculated by this method is much higher than the HIV incidence rate in either group in the study.

### 3.2. DISCOVER Efficacy Conclusions

In the DISCOVER study of Descovy versus Truvada in nearly 5400 cis-men and TGW who have sex with men at a high risk of acquiring HIV infection through sex, noninferiority of Descovy to Truvada for PrEP was established using the incidence rate ratio (0.47 [95.003% CI: 0.19, 1.15]) and a noninferiority margin of 1.62.

With 7 infections in the Descovy group and 15 infections in the Truvada group at the primary analysis data cut date, an incidence rate ratio of 0.47 for Descovy over Truvada indicates a Descovy rate of infection that is 53% lower than the Truvada rate of infection.
Compared with prior PrEP studies in MSM, the rate of incident HIV infection was lower in the DISCOVER study. Seventeen participants diagnosed with HIV during the study were most likely infected due to low adherence to study drug as determined by TFV-DP levels in RBCs, and 5 were most likely infected before study entry.

Though not statistically demonstrated in the DISCOVER study, the pharmacokinetic data provide evidence that Descovy may have an efficacy advantage over Truvada due to the higher and more rapid attainment of TFV-DP levels in PBMCs, along with the slower decay to below the protection threshold of 40 fmol per million cells, allowing for “forgiveness” in a setting of imperfect adherence.

As one measure of this, 98% of participants in the Descovy group, but only 68% of participants in the Truvada group had TFV-DP levels in PBMCs above the 40 fmol per million cells threshold at Week 4. While the 40 fmol per million cells threshold is an important target, it is not absolute, and protection against HIV acquisition may also occur at TFV-DP levels below this threshold, but at a lower rate.
4. DISCOVER SAFETY RESULTS

In the DISCOVER trial, general safety outcomes were similar between the groups, and consistent with data from clinical trials of chronic HIV treatment.

In contrast, the DISCOVER renal and bone safety outcomes were distinctly different, favoring the Descovy group, and these statistically significant differences between the Descovy and Truvada groups were also consistent with data from clinical trials of chronic HIV treatment.

4.1. General Safety Results

The safe use of Descovy for PrEP was confirmed in the DISCOVER study, a large data base of study participants using the drug daily for nearly two years. In this data base, there were no new safety risks or additional adverse drug reactions for either Descovy or Truvada identified.

Exposure

A high drug exposure was achieved in DISCOVER with an exposure of > 4300 person-years per group at the primary endpoint data cut date, and 8658 person-years overall, corresponding to a median exposure of 85.7 weeks to Descovy and 86.7 weeks to Truvada. There was a low rate of study drug discontinuations for both groups (Table 2).

| Table 2. DISCOVER: Participant Disposition (All Screened Participants) |
|-----------------------------------|---|---|---|
|                                    | DVY | TVD | Total |
| Participants Screened             |     |     | 5857  |
| Screen Failure Participants Who Were Not Randomized |     |     | 364   |
| Participants Met All Eligibility Criteria and Not Randomized<sup>a</sup> |     |     | 94    |
| Participants HIV Positive at Screening |     |     | 49    |
| Participants Randomized           | 2700| 2699| 5399  |
| Participants Randomized and Never Treated<sup>b</sup> | 6   | 6   | 12    |
| HIV Positive at Screening         | 2   | 0   | 2     |
| Participants in Safety Analysis Set | 2694| 2693| 5387  |
| Participants in Full Analysis Set (FAS) | 2670| 2665| 5335  |
| Participants Still on Study Drug up to the Data Cut Date | 2242 (83.2%) | 2263 (84.0%) | 4505 (83.6%) |
| Participants Prematurely Discontinuing Study Drug prior to the Data Cut Date | 452 (16.8%) | 430 (16.0%) | 882 (16.4%) |
| Reasons for Prematurely Discontinuing Study Drug |     |     |       |
| Adverse Event                     | 36 (1.3%) | 49 (1.8%) | 85 (1.6%) |
| Death                             | 1 (< 0.1%) | 2 (< 0.1%) | 3 (< 0.1%) |
| Investigator's Discretion         | 5 (0.2%) | 10 (0.4%) | 15 (0.3%) |
| Non-Compliance with Study Drug    | 8 (0.3%) | 12 (0.4%) | 20 (0.4%) |
### Protocol Violation
- **DVY**: 4 (0.1%)
- **TVD**: 3 (0.1%)
- **Total**: 7 (0.1%)

### Participant Decision
- **DVY**: 193 (7.2%)
- **TVD**: 175 (6.5%)
- **Total**: 368 (6.9%)

### Lost to Follow-Up
- **DVY**: 201 (7.5%)
- **TVD**: 170 (6.3%)
- **Total**: 371 (6.9%)

### Study Terminated by Sponsor
- **DVY**: 0
- **TVD**: 0
- **Total**: 0

### HIV-1 Infection
- **DVY**: 4 (0.1%)
- **TVD**: 9 (0.3%)
- **Total**: 13 (0.2%)

---

**a** Among 94 participants who met all eligibility criteria and were not randomized, the reasons (N) were: lost to follow-up (32); withdrew consent (51); investigator's discretion (3); outside of visit window (6); enrollment closed (1); participant death (1).

**b** Among 12 participants randomized but never dosed, the reasons (N) were: protocol violation (1), withdrew consent (8), HIV-1 infection (2), and investigator’s discretion (1).

Denominator for percentages is participants in the Safety Analysis Set. Screen failure participants are the participants who didn't meet all eligibility criteria.

Number screened counted by unique participant based on date of birth, race, ethnicity, sex, country, and initials among participants with screening visits.

Reasons for discontinuation based on investigator assessment.

Included CRF data collected up to 31 January 2019. Still on study drug excludes participants who have permanently discontinued study drug.

### Adverse Events

The overall frequency of reported AEs was balanced by treatment group (Table 3). Most AEs were Grade 1 or 2 in severity, and both Descovy and Truvada had low and comparable rates of notable events, such as Grade 3 or 4 AEs, SAEs, study drug-related (per investigator) AEs or SAEs, and AEs leading to study drug discontinuation.

There were two treatment-emergent deaths, one in each group (Descovy: road traffic accident; Truvada: unknown cause), neither of which was considered related to the study drugs by the investigator.

### Table 3. DISCOVER: Overall Summary of Adverse Events (Safety Analysis Set)

<table>
<thead>
<tr>
<th>Participants with the following (n, %):</th>
<th>DVY (N = 2694)</th>
<th>TVD (N = 2693)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Emergent Adverse Event</td>
<td>2498 (92.7%)</td>
<td>2494 (92.6%)</td>
</tr>
<tr>
<td>Grade 2, 3, or 4 Treatment-Emergent Adverse Event</td>
<td>1259 (46.7%)</td>
<td>1212 (45.0%)</td>
</tr>
<tr>
<td>Grade 3 or 4 Treatment-Emergent Adverse Event</td>
<td>167 (6.2%)</td>
<td>153 (5.7%)</td>
</tr>
<tr>
<td>Treatment-Emergent Study Drug-Related Adverse Event</td>
<td>545 (20.2%)</td>
<td>630 (23.4%)</td>
</tr>
<tr>
<td>Grade 2, 3, or 4 Treatment-Emergent Study Drug-Related Adverse Event</td>
<td>87 (3.2%)</td>
<td>111 (4.1%)</td>
</tr>
<tr>
<td>Grade 3 or 4 Treatment-Emergent Study Drug-Related Adverse Event</td>
<td>8 (0.3%)</td>
<td>13 (0.5%)</td>
</tr>
<tr>
<td>Treatment-Emergent Serious Adverse Event</td>
<td>169 (6.3%)</td>
<td>138 (5.1%)</td>
</tr>
<tr>
<td>Treatment-Emergent Study Drug-Related Serious Adverse Event</td>
<td>3 (0.1%)</td>
<td>5 (0.2%)</td>
</tr>
<tr>
<td>Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation</td>
<td>36 (1.3%)</td>
<td>49 (1.8%)</td>
</tr>
<tr>
<td>Treatment-Emergent Death</td>
<td>1 (&lt; 0.1%)</td>
<td>1 (&lt; 0.1%)</td>
</tr>
</tbody>
</table>

Severity grades were defined by the Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Most of the common AEs were bacterial STIs, with the most common being anal chlamydia infection, oropharyngeal gonococcal infection, and rectal gonorrhea (Table 4), likely due to the fact that ≥ 57% of participants were diagnosed with at least 1 gonorrhea or chlamydia STI at some point during the study. Other common AEs included diarrhea, nasopharyngitis, and upper respiratory tract infections. These results contrast with findings seen in HIV-1 treatment clinical trials, and reflect both the DISCOVER treatment population and the frequent STI testing used in the study regardless of symptoms.

Table 4. DISCOVER: Adverse Events Reported for at Least 10% of Participants in Either Treatment Group (Safety Analysis Set)

<table>
<thead>
<tr>
<th>Participants with the following (n, %):</th>
<th>DVY (N = 2694)</th>
<th>TVD (N = 2693)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Emergent Adverse Event</td>
<td>2498 (92.7%)</td>
<td>2494 (92.6%)</td>
</tr>
<tr>
<td>Treatment-Emergent Adverse Event by Preferred Term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anal chlamydia infection</td>
<td>770 (28.6%)</td>
<td>792 (29.4%)</td>
</tr>
<tr>
<td>Oropharyngeal gonococcal infection</td>
<td>740 (27.5%)</td>
<td>722 (26.8%)</td>
</tr>
<tr>
<td>Proctitis gonococcal</td>
<td>693 (25.7%)</td>
<td>671 (24.9%)</td>
</tr>
<tr>
<td>Exposure to communicable disease</td>
<td>465 (17.3%)</td>
<td>441 (16.4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>430 (16.0%)</td>
<td>422 (15.7%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>350 (13.0%)</td>
<td>355 (13.2%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>356 (13.2%)</td>
<td>310 (11.5%)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>342 (12.7%)</td>
<td>321 (11.9%)</td>
</tr>
<tr>
<td>Urethritis chlamydial</td>
<td>280 (10.4%)</td>
<td>259 (9.6%)</td>
</tr>
</tbody>
</table>

Preferred terms are presented by descending order of the total frequencies. Multiple AEs were counted only once per participant per preferred term.

Study drug-related (per investigator) AEs were reported for 20.2% of participants in the Descovy group, and 23.4% of participants in the Truvada group. The type and frequency of study drug-related AEs were low and balanced between the 2 groups and reflected the most common AEs in HIV and hepatitis B virus (HBV) treatment trials. Study drug-related AEs reported in at least 1% of participants in either group were: diarrhea (Descovy 5.0%; Truvada 5.9%), nausea (Descovy 4.2%; Truvada 4.6%), headache (Descovy 2.2%; Truvada 2.1%), fatigue (Descovy 1.6%; Truvada 2.7%), abdominal pain (Descovy 1.0%; Truvada 1.3%), flatulence (Descovy 0.8%; Truvada 1.2%), and abdominal discomfort (Descovy 0.7%; Truvada 1.1%).
Clinical Laboratory Evaluations

Most laboratory abnormalities were Grade 1 or 2 and consistent with those reported in clinical trials of chronic HIV and HBV treatment, and no new unexpected laboratory abnormalities were reported. Both groups had low rates of Grade 3 or 4 laboratory abnormalities and few participants in either treatment group had Grade 3 or 4 transaminase elevations. Grade 3 or 4 laboratory abnormalities reported in at least 1% of participants in either group were: increased alanine aminotransferase (Descovy 1.5%; Truvada 1.5%), increased amylase (Descovy 1.3%; Truvada 1.7%), increased aspartate aminotransferase (Descovy 2.4%; Truvada 1.9%), hyperglycemia (nonfasting) (Descovy 0.6%; Truvada 1.2%), increased low-density lipoprotein (fasting) (Descovy 2.2%; Truvada 0.8%), glycosuria (Descovy 0.7%; Truvada 1.2%).

Predefined Safety Endpoints

Descovy was superior to Truvada on all 6 prespecified alpha-controlled secondary safety endpoints, which included hip BMD, spine BMD, urine beta-2-microglobulin to creatinine ratio, urine RBP to creatinine ratio, categorical UPCR, and serum creatinine. These 6 key secondary endpoints were tested in a sequential order using the fallback procedure with alpha spent as described in Section 2.2.5.

Since the DISCOVER study included participants who were experienced in the use of Truvada for PrEP, there are also data on 905 participants who were using PrEP at study entry. In general, participants randomized to Descovy for PrEP who had previously been using Truvada for PrEP had significant improvements in their glomerular and tubular renal function, as well as in measures of hip BMD.

4.2. Renal Safety

The key renal secondary endpoints from DISCOVER study are presented in this section as well as a summary of the renal AEs.

Renal glomerular and tubular function was assessed by UPCR which detects total urinary protein due to glomerular and/or tubular pathology. Values > 200 mg/g reflect clinically significant proteinuria.

Proximal tubular dysfunction can be assessed by the ability of the kidney to filter and reabsorb the two low molecular weight proteins (< 25,000 Daltons), beta-2-microglobulin and RBP, both of which are freely filtered through the glomeruli of a healthy kidney and reabsorbed by the proximal tubules. Increases in urinary levels of these proteins, or a higher protein to serum creatinine ratio, indicates proximal renal tubular dysfunction.
Renal Safety with PrEP in DISCOVER Study

After 8658 patient years of exposure to study drug in DISCOVER, there were no cases of tubulopathy-related AEs for participants receiving Descovy in DISCOVER, whereas 1 case of Fanconi syndrome acquired indicative of proximal renal tubulopathy was reported for Truvada. The AE of Fanconi syndrome acquired was considered study drug related (per investigator), and study drugs were discontinued.

There were fewer renal and urinary disorder AEs leading to premature discontinuation of study drugs for Descovy (2 participants) compared with Truvada (6 participants). Renal-associated investigation AEs leading to premature discontinuation of study drug were reported in 3 participants in the Descovy group and 2 participants in the Truvada group. The incidence of renal and urinary disorder or renal associated investigation AEs leading to premature discontinuation of study drugs or study drug-related (per investigator) SAEs was low for both treatment groups.

Biomarkers of glomerular and tubular renal function showed statistically significant differences favoring Descovy on all 4 prespecified endpoints at Week 48 (Table 5).

Participants in the Descovy group had a 1.8 mL/min increase in eGFRCG (and corresponding 0.01 mL/dL decrease in serum creatinine) at Week 48, compared to a 2.3 mL/min decrease (and corresponding 0.01 mL/dL increase) for Truvada (Figure 8 and Figure 9). The differences were apparent by Week 4 and continued through Week 48.

Additionally, fewer participants receiving Descovy (21.3%) than Truvada (24.3%) (p = 0.009) developed dipstick proteinuria or clinically significant quantitative proteinuria at Week 48 (worsening UPCR shift to > 200 mg/g: Descovy 0.7%, Truvada 1.5%; p = 0.005 for the differences between groups in distributions of UPCR ≤ 200 mg/g versus > 200 mg/g).

The two low molecular weight proteins that are specific to proximal renal tubular function (beta-2-microglobulin and RBP) had results that remained stable for those on Descovy, whereas protein spillage and higher protein to creatinine ratios occurred for those on Truvada (Figure 10). At Week 48, there was a decrease from baseline for urine beta-2-microglobulin to creatinine ratio for Descovy (−10.7%) compared to an increase for Truvada (15.3%; p < 0.001 for the difference between groups). In addition, the Descovy group had a stable urine RBP to creatinine ratio (0.2%) while the Truvada group had a median percentage increase from baseline (19.9%; p < 0.001 for the difference between groups).

The observed early changes in the renal biomarkers correlate with fewer clinical renal events in those taking Descovy compared with Truvada \{Arribas 2017b, Gupta 2019\}. 
Table 5. DISCOVER: Key Assessments of Renal Function (Observed Data; Safety Analysis Set)

<table>
<thead>
<tr>
<th></th>
<th>DVY (N = 2694)</th>
<th>TVD (N = 2693)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine beta-2-microglobulin to Urine Creatinine ratio (µg/g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change at Week 48</td>
<td>−10.7 (−42.0, 25.9)</td>
<td>15.3 (−23.0, 97.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Change at Week 96</td>
<td>−17.2 (−47.6, 19.2)</td>
<td>11.0 (−26.8, 88.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine RBP to Urine Creatinine ratio (µg/g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change at Week 48</td>
<td>0.2 (−24.9, 35.4)</td>
<td>19.9 (−13.0, 68.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Change at Week 96</td>
<td>−2.1 (−31.0, 33.3)</td>
<td>19.9 (−16.1, 73.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Percentage of Participants who Developed UPCR &gt;200 mg/g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At Week 48</td>
<td>0.7%</td>
<td>1.5%</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>At Week 96</td>
<td>1.3%</td>
<td>1.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change at Week 48</td>
<td>−0.01 (0.107)</td>
<td>0.01 (0.111)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Change at Week 96</td>
<td>0.01 (0.116)</td>
<td>0.02 (0.116)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>eGFRCG (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change at Week 48</td>
<td>1.8 (−7.2, 11.1)</td>
<td>−2.3 (−10.8, 7.2)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Change at Week 96</td>
<td>−0.6 (−11.2, 9.7)</td>
<td>−4.1 (−13.1, 5.4)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Proteinuria by Urinalysis (Dipstick) (%)</td>
<td>21.3</td>
<td>24.3</td>
<td>p = 0.009</td>
</tr>
<tr>
<td>Number of Participants Experiencing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Any Renal and Urinary Disorder AEs Leading to Premature Discontinuation of Study Drugs</td>
<td>2</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>• Renal Associated Investigation AEs Leading to Premature Discontinuation of Study Drugs</td>
<td>3</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>• Renal and Urinary Disorder SAEs Considered by the Investigator to be Related To Study Drugs</td>
<td>1</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Number of Participants Experiencing a Proximal Renal Tubulopathy-Related AE</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant
a Mean (SD) changes from baseline
b p-values were from the ANCOVA model including baseline F/TDF for PrEP and treatment as fixed effects and baseline serum creatinine as a covariate
c Median (Q1, Q3) changes from baseline
d p-values were from the Van Elteren test stratified by baseline F/TDF for PrEP to compare the 2 treatment groups.
e Treatment-emergent graded abnormalities
f p-values for treatment comparison were from the rank analysis of covariance adjusting for baseline category and baseline F/TDF for PrEP
g Based on N who had normal UPCR (≤ 200 mg/g) at baseline
h p-value was from the Fisher exact test to compare the 2 treatment groups
i The 4 key secondary renal endpoints at Week 48 (percentage change from baseline in beta-2-microglobulin to creatinine ratio, percentage change from baseline in RBP to creatinine ratio, distribution of UPCR categories, and change from baseline in serum creatinine) are presented in the order of alpha spent.

At least 50% of participants had 96 weeks of follow-up after randomization Observed on-treatment data collected up to 30 days after last dose of study drug or all postbaseline data for participants still on study drug.
Figure 8. DISCOVER: Estimated Glomerular Filtration Rate by the Cockcroft-Gault Method

Q = quartile
p-values from Van Elteren test stratified by baseline Truvada for PrEP to compare treatment groups.

Figure 9. DISCOVER: Serum Creatinine
**Figure 10. DISCOVER: Proximal Tubular Function, Retinol Binding to Creatinine Ratio and Beta-2-microglobulin to Creatinine Ratio**

p-values from Van Elteren test stratified by baseline Truvada for PrEP to compare 2 treatment groups.

**Improvement in Renal Function Switching from Truvada to Descovy**

Improved renal safety profiles were seen for participants who had been taking Truvada for PrEP at baseline who were then randomized to receive Descovy for PrEP in DISCOVER. These results are consistent with observations in those who switched from FTC/TDF- to FTC/TAF-containing regimens in chronic HIV treatment trials.

The baseline characteristics of the 16.8% of participants on baseline Truvada differed from the overall population by being slightly older (median age for baseline Truvada for PrEP group, 36 years; overall population, 34 years), having a higher proportion with > 2 condomless anal sex partners in the past 12 weeks (baseline Truvada for PrEP: 72.0%, overall population: 61.3%), having a higher proportion with rectal chlamydia infection (baseline Truvada for PrEP: 15.9%, overall population: 12.5%), and a similar proportion who reported binge drinking (baseline Truvada for PrEP: 22.3%, overall population: 22.8%).

Participants taking Truvada for PrEP at baseline who were randomized to receive Descovy in DISCOVER, had increases in eGFR\textsubscript{CG} starting at Week 4, with continued decreases seen in those randomized to Truvada (p < 0.001 for the difference between groups at Week 48). The 3.9 mL/min median increase in eGFR\textsubscript{CG} seen at Week 48 for this subpopulation receiving Descovy was notably larger than that seen for the overall Descovy population at the same time point (1.8 mL/min).

Participants taking Truvada for PrEP at baseline who were randomized to receive Descovy in DISCOVER, also had decreases in both urine beta-2-microglobulin to creatinine ratio and urine RBP to creatinine ratio starting from Week 4, with little change, smaller decreases, or increases from baseline in those who remained on Truvada. Median percentage changes in urine beta-2-microglobulin to creatinine ratio from baseline at Week 48 were as follows: Descovy −27.1%, Truvada −5.1% (p < 0.001). Median percentage changes in urine RBP to
creatinine ratio from baseline at Week 48 were as follows: Descovy −8.6%, Truvada 11.3% (p < 0.001).

The renal biomarker changes in the 83% of the PrEP-naive participants were similar to the overall DISCOVER study results.

### 4.3. Bone Safety

The key bone secondary endpoints from DISCOVER study are presented in this section as well as a summary of fracture AEs.

**Bone Safety with PrEP in DISCOVER Study**

In DISCOVER, the proportion of participants at increased risk of BMD loss included the following:

- Age ≥ 50 years: 716 participants (13.3%)
- Age > 65 years: 53 participants (1.0%)
- Preexisting osteopenia/osteoporosis among BMD substudy participants:
  - Hip: osteopenia 90 participants (24.0%); osteoporosis 1 participant (0.3%)
  - Spine: osteopenia 96 participants (25.4%); osteoporosis 10 participants (2.6%)

Hip and spine BMD were prespecified as key secondary safety endpoints in DISCOVER.

Overall, participants in the Descovy group in DISCOVER had improved bone safety as compared with those in the Truvada group.

Fracture AEs were reported for 2.0% of participants in each group, with most occurring as a result of trauma as assessed by the medical monitor. There were 3 nontraumatic fractures as follows: 1 participant in the Descovy group (cervical vertebral fracture) and 2 participants in the Truvada group (shoulder and metatarsal fractures). All nontraumatic fractures were in participants older than 50 years, who did not have a prior history of osteopenia or osteoporosis, and who were not included in the BMD substudy. The Truvada participant with the metatarsal fracture had significant BMD loss and received supplemental calcium and vitamin D as prophylaxis of osteoporosis. No nontraumatic fracture was considered serious, study drug related, or led to study drug discontinuation.

In the BMD substudy of DISCOVER drug exposure was 328 person-years for the Descovy group and 330 person-years for the Truvada group. There was a median exposure of 96 weeks to both Descovy and Truvada. The general DISCOVER population had a median age of 34 years, while the BMD substudy had a median age of 37 years, suggesting that in both the overall DISCOVER study and in the BMD substudy, almost half of the participants may still be building to peak bone mass. This is relevant for interpreting the BMD substudy results.
The 2 prespecified bone safety endpoints showed statistically significant differences favoring Descovy over Truvada (Table 6). At Week 48, participants receiving Descovy had increases in mean spine BMD (0.50%) from baseline and stable hip BMD (0.18%), whereas those receiving Truvada had declines in spine (−1.12) and hip BMD (−0.99) from baseline; differences between groups were statistically significant for both measures. Categorical changes in BMD were also more favorable for Descovy than for Truvada with significantly fewer participants in the Descovy group having a BMD decrease of at least 3% (Table 7).

Table 6. DISCOVER: Percentage Changes from Baseline in Hip and Spine BMD at Weeks 48 (Observed Data; Hip and Spine DXA Analysis Sets)

<table>
<thead>
<tr>
<th></th>
<th>DVY</th>
<th>TVD</th>
<th>DVY vs. TVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>p-value</td>
</tr>
<tr>
<td>Hip BMD*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (g/cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>190</td>
<td>185</td>
<td>0.60</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.029 (0.1542)</td>
<td>1.021 (0.1322)</td>
<td></td>
</tr>
<tr>
<td>% Chg at Week 48</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>N</td>
<td>158</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.183 (2.3841)</td>
<td>-0.988 (2.4351)</td>
<td></td>
</tr>
<tr>
<td>Spine BMDb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (g/cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>190</td>
<td>188</td>
<td>1.00</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.131 (0.1615)</td>
<td>1.131 (0.1380)</td>
<td></td>
</tr>
<tr>
<td>% Chg at Week 48</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>N</td>
<td>159</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.496 (2.9883)</td>
<td>-1.123 (2.9446)</td>
<td></td>
</tr>
</tbody>
</table>

a Only participants with nonmissing baseline hip BMD were included in Hip DXA Analysis Set.
b Only participants with nonmissing baseline spine BMD were included in Spine DXA Analysis Set.
Observed on-treatment data collected up to 30 days after last dose of study drug or all postbaseline data for participants still on study drug.

% Chg (Percentage Change) = Change from baseline at a postbaseline visit/baseline * 100%
P-values, difference in least-squares means (Diff in LSM), and its 95% CI were from the ANOVA model with baseline F/TDF for PrEP and treatment as fixed effects.
### Table 7. DISCOVER: Key Measures of BMD at Week 48 (Observed Data; Hip and Spine DXA Analysis Sets)

<table>
<thead>
<tr>
<th></th>
<th>DVY</th>
<th>TVD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hip DXA Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants with Categorical Change (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3% Decrease in BMD</td>
<td>3.8%</td>
<td>18.4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No Decrease</td>
<td>50.0%</td>
<td>34.2%</td>
<td>0.006</td>
</tr>
<tr>
<td>≥ 3% Increase in BMD</td>
<td>8.9%</td>
<td>6.3%</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Spine DXA Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants with Categorical Change (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3% Decrease in BMD</td>
<td>10.1%</td>
<td>26.9%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No Decrease</td>
<td>61.0%</td>
<td>32.5%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ 3% Increase in BMD</td>
<td>17.0%</td>
<td>9.4%</td>
<td>0.052</td>
</tr>
</tbody>
</table>

*Only participants with nonmissing % change from baseline BMD were included in the DXA Analysis Sets.

<table>
<thead>
<tr>
<th></th>
<th>DVY</th>
<th>TVD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hip DXA Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants with Categorical Change (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3% Decrease in BMD</td>
<td>3.8%</td>
<td>18.4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No Decrease</td>
<td>50.0%</td>
<td>34.2%</td>
<td>0.006</td>
</tr>
<tr>
<td>≥ 3% Increase in BMD</td>
<td>8.9%</td>
<td>6.3%</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Spine DXA Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants with Categorical Change (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3% Decrease in BMD</td>
<td>10.1%</td>
<td>26.9%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No Decrease</td>
<td>61.0%</td>
<td>32.5%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ 3% Increase in BMD</td>
<td>17.0%</td>
<td>9.4%</td>
<td>0.052</td>
</tr>
</tbody>
</table>

*For each category, p-value was based on a dichotomized response (ie, ≥ 3% vs. < 3% Decrease) from the CMH test for nominal data (general association statistic) adjusting for baseline F/TDF for PrEP.

Observed on-treatment data collected up to 30 days after last dose of study drug or all postbaseline data for participants still on study drug.

Percentage change = change from baseline at a postbaseline visit/baseline * 100%

No Decrease means "≥ 0% Increase".

There were no differences between groups in participants taking or initiating osteoporosis medications.

**Improvement in BMD Switching from Truvada to Descovy**

Of the 383 participants in the BMD substudy in DISCOVER, only 53 were taking baseline Truvada for PrEP, thus limiting statistical power to determine any differences between those who were then randomized to Descovy and those who were randomized to Truvada. However, data indicate bone safety advantages for those who were randomized to Descovy (n = 23). While there were no between group differences at Week 48 between Descovy and Truvada in either spine or hip BMD, there was a statistically significant within group improvement of 1.13% in hip BMD in the baseline Truvada users who were randomized to Descovy (Table 8).
Table 8. DISCOVER: Percentage Changes from Baseline in Hip and Spine BMD at Weeks 48 for Participants on Baseline Truvada (Observed Data; Hip and Spine DXA Analysis Sets)

<table>
<thead>
<tr>
<th></th>
<th>DVY</th>
<th>TVD</th>
<th>DVY vs. TVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>p-value&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Hip BMD</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (g/cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>26</td>
<td>27</td>
<td>0.41</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>0.994 (0.937, 1.062)</td>
<td>0.986 (0.913, 1.051)</td>
<td></td>
</tr>
<tr>
<td>% Chg at Week 48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>23</td>
<td>19</td>
<td>0.46</td>
</tr>
<tr>
<td>Median (SD)</td>
<td>1.129 (−0.861, 3.471)</td>
<td>0.500 (−0.751, 3.068)</td>
<td></td>
</tr>
<tr>
<td>p-value for percentage change from baseline&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.027</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td><strong>Spine BMD</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (g/cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>26</td>
<td>27</td>
<td>0.47</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>1.126 (0.990, 1.211)</td>
<td>1.093 (0.999, 1.152)</td>
<td></td>
</tr>
<tr>
<td>% Chg at Week 48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>23</td>
<td>19</td>
<td>0.46</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>0.000 (−1.839, 3.436)</td>
<td>−0.601 (−2.300, 1.614)</td>
<td></td>
</tr>
<tr>
<td>p-value for percentage change from baseline&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.58</td>
<td>0.62</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Only participants with nonmissing baseline hip BMD were included in Hip DXA Analysis Set.

<sup>b</sup> Only participants with nonmissing baseline spine BMD were included in Spine DXA Analysis Set.

<sup>c</sup> p-value for between group comparison were from the ANOVA model including treatment as a fixed effect.

<sup>d</sup> p-value for percentage change from baseline within treatment group were from the Wilcoxon sign rank test.

Observed on-treatment data collected up to 30 days after last dose of study drug or all postbaseline data for participants still on study drug.

% Chg (Percentage Change) = Change from baseline at a postbaseline visit/baseline * 100%

P-values were from the ANOVA model including treatment as a fixed effect.

Baseline F/TDF for PrEP defined as F/TDF taken without any third agent and end date between Screening and first dose date (inclusive).

**BMD in Participants Aged Less than 25 Years**

In participants less than 25 years of age, participants receiving Descovy had increases in mean hip (0.29%) and spine (0.36%) BMD from baseline at Week 48; whereas those receiving Truvada had declines in hip (−2.24%) and spine (−2.38%) BMD from baseline; differences between groups were statistically significant for both measures (p = 0.015 for hip and p = 0.021 for spine for the difference between groups). The losses at Week 48 in the Truvada group of over two percent are striking as participants aged < 25 years would be expected to still be building
bone and increasing their BMD. These findings highlight the clinical significance of the Descovy bone safety advantage.

### 4.4. Sexually Transmitted Infections

There are conflicting reports in the PrEP literature regarding whether PrEP initiation is associated with “risk compensation”, an increase in risk behaviors when a new prevention method is adopted {Blumenthal 2014}. This theory comes from a behavioral concept that individuals have risk homeostasis—such that if they adopt a prevention or risk lowering behavior, they may compensate by increasing their risk behavior.

To assess risk compensation in the DISCOVER study, incidence of STIs was rigorously monitored in this population. Participants reported their sexual behaviors via CASI. Sexually transmitted infections were also evaluated at screening, Week 4, Week 12, and every 12 weeks with laboratory testing for 3 anatomic sites for gonorrhea and chlamydia, as well as serologic syphilis testing. In addition, the incidence of investigator reported STIs or exposure to STIs as AEs were compiled to capture any STIs diagnosed outside the study or between study visits, and any exposure to STIs from participant’s partners. Sexually transmitted infection treatment data was also collected via concomitant medications.

The rates of self-reported sexual behavior and STIs reported as AEs (Section 4.1), including rectal STIs, on-study were high, persistent, and similar between the Descovy and Truvada groups. This demonstrated continued high-risk behavior and a lack of risk compensation for all study participants.

The mean number of condomless receptive anal sex partners was high at baseline and remained high throughout the study, with no differences between the Descovy and Truvada groups. A mean of approximately 4 condomless anal sex partners was self-reported for each 12-week period (Figure 11). Around 61% of participants in each group reported more than 2 condomless anal sex partners in the past 12 weeks at screening and about 50% continued to report more than 2 throughout the study.

**Figure 11.** DISCOVER: Number of Condomless Receptive Anal Sex Partners by Visit (A); Participants with ≥ 2 Condomless Receptive Anal Sex Partners (B)

SD = standard deviation.

a Collection interval at Week 12 was from Week 4 to Week 12.
Laboratory assessed STI data mirrored the self-report of sexual behavior and AE data. The rates of gonorrhea and chlamydia at any of the 3 anatomic sites tested were high and persistent throughout the study; approximately 15% of participants in each group had these STIs at each visit during the study (Figure 12). Laboratory assessed rectal gonorrhea and chlamydia were similarly high and persistent through the study. Approximately 10% of participants in each group had rectal gonorrhea or chlamydia at baseline and at each visit through the study (Figure 13).

Figure 12. DISCOVER: Incidence of Any Gonorrhea or Chlamydia (Laboratory Data) Over Time by Treatment (Full Analysis Set)

Figure 13. DISCOVER: Rectal Gonorrhea and Chlamydia (Rectal NAAT Testing by Study Visit)
The laboratory-based incidence rates of gonorrhea, chlamydia, and syphilis were similarly high (Table 9). The overall rectal gonorrhea incidence rate was 21.0 per 100 person-years, which correlates with an expected HIV incidence of approximately 6.7 per 100 person-years, much higher than what was reported in DISCOVER {Mullick 2019}.

Table 9. DISCOVER: Number of Participants Having Gonorrhea, Chlamydia, and Syphilis and Incidence Rate (Local or Central Laboratory Data) (Full Analysis Set)

<table>
<thead>
<tr>
<th>Number of Participants with STI (incidence Rate per 100 Person-Years)</th>
<th>DVY (N = 2670)</th>
<th>TVD (N = 2665)</th>
<th>Total (N = 5335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhea</td>
<td>1053 (47.1)</td>
<td>1059 (45.3)</td>
<td>2112 (46.2)</td>
</tr>
<tr>
<td>Rectal Gonorrhea</td>
<td>651 (21.6)</td>
<td>662 (20.5)</td>
<td>1313 (21.0)</td>
</tr>
<tr>
<td>Pharyngeal Gonorrhea</td>
<td>744 (22.2)</td>
<td>726 (21.1)</td>
<td>1470 (21.6)</td>
</tr>
<tr>
<td>Urethral Gonorrhea</td>
<td>129 (3.4)</td>
<td>142 (3.6)</td>
<td>271 (3.5)</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>1049 (41.9)</td>
<td>1071 (41.6)</td>
<td>2120 (41.7)</td>
</tr>
<tr>
<td>Rectal Chlamydia</td>
<td>810 (27.5)</td>
<td>835 (28.2)</td>
<td>1645 (27.9)</td>
</tr>
<tr>
<td>Pharyngeal Chlamydia</td>
<td>197 (5.1)</td>
<td>171 (4.3)</td>
<td>368 (4.7)</td>
</tr>
<tr>
<td>Urethral Chlamydia</td>
<td>335 (9.2)</td>
<td>324 (9.1)</td>
<td>659 (9.1)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>365 (10.3)</td>
<td>370 (9.5)</td>
<td>735 (9.9)</td>
</tr>
</tbody>
</table>

Rectal and pharyngeal results based on local laboratory tests. Urethral results based on central laboratory tests. Syphilis results based on investigator reported cases of syphilis diagnosis with status of new, reinfection or missing (excluding syphilis treatment failures).

The AE-based incidence rates of gonorrhea, chlamydia, and syphilis were even higher with incidence rates of 145 per 100 person-years in the Descovy group and 139 per 100 person-years in the Truvada group, potentially reflecting that STI events diagnosed outside of the study, as well as in between study follow-up visits, were included. There were no differences between Descovy and Truvada in the incidence of rectal and all types of STIs, gonorrhea, chlamydia, and syphilis.

The most common concomitant medications used by participants were azithromycin, ceftriaxone / ceftriaxone sodium, and doxycycline which are all used to treat STIs (Table 10).
Table 10. DISCOVER: Concomitant Medications Used by > 10% of Participants

<table>
<thead>
<tr>
<th>Drug</th>
<th>DVY (N = 2694)</th>
<th>TVD (N = 2693)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>1604 (59.5)</td>
<td>1538 (57.1)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>868 (32.2)</td>
<td>822 (30.5)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>785 (29.1)</td>
<td>765 (28.4)</td>
</tr>
<tr>
<td>Ceftriaxone sodium</td>
<td>549 (20.4)</td>
<td>579 (21.5)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>513 (19.0)</td>
<td>502 (18.6)</td>
</tr>
<tr>
<td>Vitamins not otherwise specified</td>
<td>481 (17.9)</td>
<td>468 (17.4)</td>
</tr>
<tr>
<td>Benzathine Benzylpenicillin</td>
<td>385 (14.3)</td>
<td>376 (14.0)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>389 (14.4)</td>
<td>317 (11.8)</td>
</tr>
</tbody>
</table>

Concomitant non-antiretroviral medications during study were non-antiretroviral medications used between the first dose and the last dose dates of study drug (inclusive). Participants were counted only once for each preferred drug name.

4.5. Other Safety Outcomes

Lipids

There were minimal changes in fasting lipids in the Descovy group and small decreases for Truvada (p ≤ 0.002; Figure 14). There was no difference in the mean change in total cholesterol: high-density lipoprotein ratio, which is associated with cardiovascular mortality {Anderson 1991}, between Descovy and Truvada at Week 48 {Arribas 2017b}.

Figure 14. DISCOVER: Fasting Lipid Changes from Baseline at Week 48

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups. HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Body Weight

Approximately 50% of participants in both groups were in the overweight body mass index category at baseline. Participants in the Truvada group had stable weight, whereas those in the Descovy group had a mean increase of 1.1 kg at Week 48, which is similar to the average weight gained by an American aged 20 to 40 years over 1 year {Hill 2003} and the placebo arms of two placebo-controlled PrEP studies in HIV-uninfected participants {Glidden 2018, RJ 2019}. Consistent with data collected outside of the DISCOVER study, these results suggest that Truvada may suppress weight whereas the weight change in the Descovy group is similar to average American weight gain and the weight gain in placebo arms of two different PrEP trials.

4.6. Safety Conclusions

With over 1.3 million person-years of clinical experience and > 20,000 person-years of clinical trial experience, the safety profile of Descovy is well-characterized.

Descovy is safe and well tolerated. In clinical trials of chronic HIV treatment, the only known adverse drug reaction for Descovy is nausea {DESCOVY® 2017}. Descovy has been demonstrated to have superior renal and bone safety in the treatment of HIV and HBV infection.

Some populations at risk of HIV infection may be at increased risk of reduced BMD including young adults aged under 35 years who are still building bone, those with pre-existing osteopenia or osteoporosis, women, and those under 35 years or over 50 years of age {Pilkington 2018, Walsh 2009, Weaver 2016}. Reduced mineralization (low peak BMD) is a problem tied with future risk of osteopenia and osteoporosis. Peak BMD occurs between the ages of 25 and 35 years, and the magnitude of peak bone mass is a predictor of fracture risk and osteoporosis later in life {Weaver 2016}. In addition, drug-induced BMD reductions (~1.85% at 24 months) in early adulthood have led to increased fracture risk later in life: depot medroxyprogesterone acetate causes moderate reductions in BMD and is associated with fracture risk later in life {Kyvernitakis 2017, Lara-Torre 2004}.

In DISCOVER, Descovy was superior to Truvada on all 6 prespecified bone and renal safety endpoints. There were low rates of SAEs or AEs leading to discontinuation of study drug in either group, however Descovy had significantly better bone and renal safety compared with Truvada. In addition, bone and renal improvements were seen for participants taking Truvada for PrEP at baseline who were then randomized to receive Descovy for PrEP in DISCOVER. There was no evidence of risk compensation as rates of condomless anal sex and STIs were high and persistent throughout the study with no differences between Descovy and Truvada.

The renal safety advantage of Descovy is of particular importance for those over 50 years of age who may have age-related eGFR reduction and be at risk of renal disease, and those who have preexisting comorbidities such as diabetes or hypertension.

The safety advantages of Descovy over Truvada seen in the DISCOVER study in people at risk of HIV are consistent with the Descovy safety profile from clinical trials and real-world experience with 1.1 million people worldwide living with HIV receiving treatment with TAF-containing regimens {Arribas 2017b, Kasonde 2014, Liu 2011, Sax 2015}.
The DISCOVER results are the first demonstration that these well-understood renal and bone safety advantages of Descovy over Truvada are also true for the HIV-uninfected population who have no significant medical problems. Of note, the bone mineralization and renal safety advantages of Descovy compared with Truvada are more apparent in the DISCOVER study compared to the HIV treatment program. This is most likely due to the lack of HIV-related comorbidities and lack of potent third agents when FTC/TAF is used as a backbone as part of a complete HIV treatment regimen.

The results from DISCOVER represent a significant development for Descovy for PrEP from a clinical perspective; those at risk of HIV may now opt for a similarly efficacious but safer drug.
5. EXTRAPOLATION OF DATA TO CIS-WOMEN AND ADOLESCENTS

5.1. Background on Extrapolation to Cis-women and Adolescents

Recognizing the importance of providing at risk populations the opportunity to use Descovy for PrEP, a multifactorial strategy was developed with input from FDA and in alignment with regulatory precedence and guidance (U. S. Department of Health and Human Services 2014, U. S. Department of Health and Human Services 2015, U. S. Department of Health & Human Services (DHHS) 2019), to bridge nonclinical, pharmacokinetic/pharmacodynamic, and clinical efficacy and safety data to support an indication for populations who were not enrolled in the DISCOVER study.

This data extrapolation was designed to provide a foundation of evidence for the use of Descovy for PrEP in 2 populations that are disproportionally represented among newly HIV-infected persons: cis-women (Section 5.2) and adolescents (Section 5.3).

5.2. Extrapolation to Cis-Women

5.2.1. Data Strategy for Cis-Women

Truvada has been shown to be highly effective for HIV PrEP in treatment-adherent cis-women (Gilead Sciences Inc. 2018, TRUVADA 2018b). The initial approval of Truvada for HIV PrEP included an indication for women, primarily based on results of the large, Phase 3, Partners PrEP study in serodiscordant heterosexual couples, in which women taking Truvada had a 66% reduction in the risk of acquiring HIV compared with placebo with an overall reduction of approximately 90% among participants with detectable drug levels (Baeten 2012a).

As described in this document, Descovy for PrEP has also been shown to be highly efficacious in the cis-men and TGW who participated in the DISCOVER study. The study data demonstrated that Descovy has noninferior efficacy and a superior bone and renal safety profile relative to Truvada. The results of the current study support the use of Descovy for populations at risk of HIV infection.

Data supporting the bridge to cis-women for the efficacy and safety of Descovy from the DISCOVER study have been collected from numerous nonclinical and clinical pharmacology, efficacy, and safety studies as briefly summarized below. The details of the relevant efficacy and safety assessments are provided in Sections 5.2.2 and 5.2.3, respectively.

Efficacy

FTC, TAF and PBMC-associated TFV-DP pharmacokinetics within Descovy are comparable between female and male HIV-uninfected healthy volunteers, and participants in DISCOVER (Section 5.2.2). Therefore, the efficacy of Descovy for PrEP may be extrapolated from the DISCOVER population to cis-women, as Truvada has been shown to have comparable PrEP efficacy in women and men in 2 clinical studies (Baeten 2012, Choopanya 2013)(Figure 15).
Furthermore, TFV-DP concentrations in cervicovaginal tissue in female volunteers are higher following steady state dosing with Descovy as compared to Truvada.

Results from a series of nonhuman primate (macaque) studies show that both TDF and TAF protect against SHIV or SIV transmission. Nonclinical study results also support use of an FTC-containing combination (ie, FTC+TAF or FTC+TAF), rather than TDF or TAF alone, and provide evidence that PBMC exposure is the most relevant correlate for PrEP protection against HIV exposure through either rectal or vaginal routes. Key nonclinical studies conducted in nonhuman primates are summarized in Appendix 9.3.

**Figure 15. Primary Extrapolation Strategy for Cis-Women**

![Diagram](image1)

- a. Male healthy volunteers from 11 Phase 1 studies
- b. Female healthy volunteers from 11 Phase 1 studies
- c. Cis-men and transgender women from DISCOVER

**Safety**

FTC and TAF pharmacokinetics within Descovy are comparable between cis-women with HIV and healthy female volunteers (Figure 16, Appendix 9.4.1). Therefore, the extensive, long-term safety database for Descovy in women supports the safety of Descovy for PrEP in cis-women at risk of HIV (Section 5.2.3).

**Figure 16. Safety Extrapolation Strategy for Cis-Women**

![Diagram](image2)

- a. Women living with HIV from 11 Phase 2 and 3 clinical studies
- b. Female healthy volunteers from 11 Phase 1 studies

### 5.2.2. Efficacy Extrapolation for Cis-Women

Summary analyses of pharmacokinetic data pooled across multiple Phase 1 clinical studies of women and men demonstrate that there are comparable systemic exposures of FTC and TAF, and PBMC-associated TFV-DP in women and men (Table 11, Table 12, Table 13, Appendix Table 11, Appendix Table 12) {Gilead Sciences Inc. 2018, TRUVADA 2018b} {Custodio 2016, Lutz 2018a}. 
Table 11. Pooled Data from Phase 1 Studies in Volunteers: Summary and Statistical Comparison of FTC Plasma Pharmacokinetic Parameters between Women and Men (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>FTC PK Parameter</th>
<th>Mean (CV%) (Q1, Q3)</th>
<th>% GLSM Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women (N = 91)</td>
<td>Men (N = 142)</td>
</tr>
<tr>
<td>AUC$_{\text{tau}}$ (h•ng/mL)</td>
<td>12,099.6 (21.2) (10349.7, 13213.4)</td>
<td>10,541.3 (15.9) (9289.3, 11482.4)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>2336.8 (21.5) (1940.0, 2620.0)</td>
<td>1942.2 (22.0) (1640.0, 2120.0)</td>
</tr>
<tr>
<td>$C_{\text{tau}}$ (ng/mL)</td>
<td>75.9 (39.3) (54.9, 84.8)</td>
<td>78.1 (24.1) (63.3, 89.0)</td>
</tr>
</tbody>
</table>

The estimates and 90% CI were from an ANCOVA model adjusted by Study ID. Data were pooled from 9 multiple-dose, Phase 1 PK studies.

Table 12. Pooled Data from Phase 1 Studies in Volunteers: Statistical Comparison of TAF Plasma Pharmacokinetic Parameters between Women and Men (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>TAF Pharmacokinetic Parameter</th>
<th>Mean (CV%) (Q1, Q3)</th>
<th>% GLSM Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women (N = 138)</td>
<td>Men (N = 161)</td>
</tr>
<tr>
<td>AUC$_{\text{tau}}$ (h•ng/mL)$^a$</td>
<td>338.5 (34.9) (250.7, 406.7)</td>
<td>255.9 (37.4) (187.1, 307.4)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>313.3 (65.9) (196.0, 383.0)</td>
<td>237.8 (59.4) (141.0, 301.0)</td>
</tr>
</tbody>
</table>

The estimates and 90% CI were from an ANCOVA model adjusted by Study ID. Data were pooled from 11 multiple-dose, Phase 1 pharmacokinetic studies.

$^a$ N = 133 women; N = 160 men for AUC$_{\text{tau}}$
Table 13. Summary of PBMC-Associated TFV-DP Pharmacokinetic Parameters for Women and Men Healthy Volunteers and for the DISCOVER Study (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>TFV-DP PK Parameter</th>
<th>Women&lt;sup&gt;a&lt;/sup&gt; Descovy (N = 42)</th>
<th>Men&lt;sup&gt;a&lt;/sup&gt; Descovy (N = 13)</th>
<th>DISCOVER Descovy N=158</th>
<th>DISCOVER Truvada N=151</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;tau&lt;/sub&gt; (h•fmol/million cells)</td>
<td>10,258.9 (5963.7, 25571.5)</td>
<td>8704.7 (7503.9, 12625.4)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>C&lt;sub&gt;tau&lt;/sub&gt; (fmol/million cells)</td>
<td>185.2 (152.1, 415.9)</td>
<td>326.5 (222.3, 465.1)</td>
<td>403.6 (225.9, 711.1)</td>
<td>60.6 (34.4, 105.3)</td>
</tr>
</tbody>
</table>

Data were pooled from 2 multiple-dose, Phase 1 pharmacokinetic studies.

The pharmacokinetics of TFV-DP in cervicovaginal and rectal tissues in women were also evaluated following single or multiple doses of TAF, Descovy, and Truvada (Table 14) {Cottrell 2017, Schwartz 2018a, Schwartz 2018b}.

In a single dose study of TAF 25 mg, cervicovaginal and rectal tissue levels of TFV-DP were often unquantifiable or low within hours of drug administration {Cottrell 2017}. In contrast, in a multiple-dose study described below in which female volunteers received steady state dosing, cervicovaginal tissue levels of TFV-DP were higher after TAF 25 mg administration (as part of Decovy) than after TDF 300 mg administration (as part of Truvada).

In a multiple-dose study of TAF 25 mg, TAF 10 mg, and TDF 300 mg, {Schwartz 2018a, Schwartz 2018b} at 4 hours after last dose, there were substantially higher steady-state TFV-DP concentrations in the vaginal tissue in HIV-uninfected women who received once-daily Descovy as compared with Truvada. In brief, a 1.9-fold higher median TFV-DP AUC (3,513,216.5 vs 1,829,989.9 h•fmol/g), 3.3-fold higher median C<sub>max</sub> (145,175.3 vs 44,277.2 fmol/g), and 6.3-fold higher C<sub>4h</sub> (151,001.7 vs 24,137.4 fmol/g) were observed following Descovy relative to Truvada.

From this same multiple-dose study in women, rectal tissue levels of TFV-DP C<sub>4h</sub> were 16.8-fold lower following Descovy relative to Truvada (150,073.6 vs 2,520,705.5 fmol/g), a finding that is similar to the lower rectal tissue concentrations observed in men using TAF relative to men using TDF (TAF 47 fmol/million cells; TDF 441 fmol/million cells {Fletcher 2019}).

Unlike in PBMCs, there are no established rectal tissue concentration thresholds that are associated with the effectiveness of HIV prevention.

The multiple-dose TAF clinical study demonstrates that TAF use leads to higher concentrations of TFV-DP once steady-state dosing in achieved. Although the relative importance of high TFV-DP levels in PBMCs and TFV-DP levels in mucosal tissues of the vagina or the rectum are not established, both may contribute to HIV prevention. Because SHIV RNA in rhesus monkeys, and presumably HIV-1 RNA in humans, traffics to local and distant lymph nodes, as well as to the intestine, lung, liver, and brain, within days after viral challenge {Liu 2016}, local tissue...
exposure likely only provides partial protection against HIV exposure at the mucosal level. The data from Anderson and colleagues show a clear correlation of the TFV-DP levels in PBMCs and protection from HIV acquisition {Anderson 2012c}.

Collectively, available pharmacokinetic data provide support that the efficacy with Descovy for PrEP in DISCOVER can be extrapolated to cis-women and would be at least comparable to that reported with use of Truvada for PrEP daily in the Phase 3 Partners PrEP study in which heterosexual women in serodiscordant relationships had a 75% reduction in HIV risk. These data provide evidence that PBMC exposure is a relevant correlate for PrEP protection against HIV exposure through either rectal or vaginal routes.

Taken together, the higher levels of the active metabolite TFV-DP in both PBMCs and vaginal tissue with Descovy relative to Truvada, provide relevant evidence that Descovy for PrEP will be effective in cis-women.
Table 14. External Clinical Pharmacology Studies: Summary of TFV and TFV-DP Pharmacokinetic Parameters in Various Biomatrices for Women

<table>
<thead>
<tr>
<th>Biomatrix and Analyte</th>
<th>Pharmacokinetic Parameter</th>
<th>Multiple-Dose Study Median (Range)</th>
<th>Single-Dose Study Median (Q1, Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>After 14 Daily Doses of Descovy (N = 24)</td>
<td>After 14 Daily Doses of Truvada (N = 25)</td>
</tr>
<tr>
<td>PBMC TFV-DP</td>
<td>AUC_{0-24} (h•fmol/10^6 cells)</td>
<td>15,214.8 (8700.0, 42,688.6)</td>
<td>2497.5 (561.7, 3993.1)</td>
</tr>
<tr>
<td></td>
<td>C_{24h} (fmol/10^6 cells)</td>
<td>523.2 (272.9, 931.3)</td>
<td>86.7 (25.0, 141.5)^a</td>
</tr>
<tr>
<td>Vaginal tissue TFV-DP</td>
<td>AUC_{0-last} (h•fmol/g)</td>
<td>3,513,216.5 (371,077.3)^b</td>
<td>1,829,989.9 (157,306.9)^b</td>
</tr>
<tr>
<td></td>
<td>C_{max} (fmol/g)</td>
<td>145,175.3 (17,372.2)^b</td>
<td>44,277.2 (5401.4)^b</td>
</tr>
<tr>
<td></td>
<td>C_{4h} (fmol/g)</td>
<td>151,001.7 (45,912.6, 212,284.8)^d</td>
<td>24,137.4 (11,596.3, 74,825.8)^d</td>
</tr>
<tr>
<td>Rectal tissue TFV-DP</td>
<td>AUC_{0-last} (h•fmol/g)</td>
<td>Not determined</td>
<td>Not determined</td>
</tr>
<tr>
<td></td>
<td>C_{max} (fmol/g)</td>
<td>Not determined</td>
<td>Not determined</td>
</tr>
<tr>
<td></td>
<td>C_{4h} (fmol/g)</td>
<td>150,073.6 (36,970.6, 708,600.5)^d</td>
<td>2,520,705.5 (322,820.1, 19,429,726.2)^e</td>
</tr>
</tbody>
</table>

*Pharmacokinetic parameters in cervical tissues were similar to those observed in vaginal tissues; therefore, only vaginal tissue pharmacokinetic parameters are included.*

- a N = 24
- b N = 4; values presented are Estimate (SE)
- c TFV-DP was quantifiable in 12.5% of vaginal tissue samples from the TAF 25 mg cohort.
- d N = 8
- e N = 9
- f TFV-DP was quantifiable in 25% of rectal tissue samples from the TAF 25 mg cohort.

### 5.2.3. Safety of Descovy in Cis-Women

As described above, pharmacokinetic analyses demonstrate that exposures of TAF, FTC, and TVF-DP are comparable between men and women following administration of FTC/TAF, and the safety profile of Descovy has also been shown to be comparable in both sexes in clinical studies. Given this, the safety results from DISCOVER (and other clinical studies of Descovy) are relevant to a cis-women PrEP population.

Further, pharmacokinetic analyses demonstrate that that HIV infection status does not alter either FTC or TAF pharmacokinetic levels in a clinically meaningful manner. As a result, the extensive safety evaluations and clinical experience of Descovy in women with HIV also provide clinical safety data that support use of Descovy for PrEP in cis-women at risk of HIV. These analyses
comparing pharmacokinetic assessments by HIV status are described for reference in Appendix 9.4.

The safety of Descovy in women living with HIV has been reported from multiple clinical development programs using TAF-based regimens {BIKTARVY® 2018a, BIKTARVY® 2018b, DESCOVY 2018, DESCOVY® 2017, Genvoya 2018b, GENVOYA® 2018b, Odefsey 2017, ODEFSEY® 2017}. No differences were noted in the safety profile for women versus the general adult population during the clinical development of Descovy and other TAF-containing products.

In clinical studies that included nearly 800 HIV-infected women, (including 260 treatment-naive women) there were significant improvements in bone and renal safety in women taking TAF-based regimens as compared to women taking TDF-based regimens (Table 15).

Consistent with the data from DISCOVER, these clinical studies in women living with HIV show that TAF-containing regimens had less impact on general and proximal renal tubular proteins (p < 0.001), and on changes in BMD (p < 0.001). Moreover, treatment-experienced women who switched from a TDF-based regimen to a TAF-based regimen had significantly less general and proximal tubular proteinuria (p < 0.001), and had significant increases in BMD (p < 0.001) after the switch.
### Table 15. Measures of Renal and Bone Safety at Week 96 (Safety Analysis Set from Pooled Analysis of 7 Phase 3 Studies)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Antiretroviral-Naive Women</th>
<th>Virologically Suppressed Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAF-Containing Regimen</td>
<td>TDF-Containing Regimen</td>
</tr>
<tr>
<td></td>
<td>(N = 133)</td>
<td>(N = 127)</td>
</tr>
<tr>
<td>n (%)</td>
<td>p-value</td>
<td>n (%)</td>
</tr>
<tr>
<td>Renal AEs</td>
<td>5 (3.8%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Dipstick proteinuria(^a)</td>
<td>38 (28.6%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Median</td>
<td>p-value</td>
<td>Median</td>
</tr>
<tr>
<td>Δ Serum Creatinine (mg/dL)</td>
<td>0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>Δ eGFR(^CG) (mL/min/1.73 m(^2))</td>
<td>−5.8</td>
<td>−8.6</td>
</tr>
<tr>
<td>% Δ UACR</td>
<td>−11.8</td>
<td>4.6</td>
</tr>
<tr>
<td>% Δ RBP:Cr</td>
<td>12.1</td>
<td>67.5</td>
</tr>
<tr>
<td>% Δ β2M:Cr</td>
<td>−37.4</td>
<td>13.3</td>
</tr>
<tr>
<td>% Δ Spine BMD(^c)</td>
<td>−0.292</td>
<td>−2.606</td>
</tr>
<tr>
<td>% Δ Hip BMD(^c)</td>
<td>−1.296</td>
<td>−3.938</td>
</tr>
</tbody>
</table>

P-values were from Wilcoxon rank sum test, except for the p-value for treatment-emergent proteinuria as Grade 0 vs Grade 1-3 and incidence of renal AEs, which were from the Fisher exact test. Renal AEs were defined by selected preferred terms under the SOC of Renal and Urinary Disorders based on clinical review.  
\(^a\) The denominator for percentages was the number of participants in the Safety Analysis Set with at least 1 post baseline value for urine protein.  
\(^b\) Week 96 data were used for all but 1 study, which used Week 48 data.  
\(^c\) These data were pooled from 6 studies. (One study did not have BMD data available.)

Among 260 treatment-naive women receiving long-term TAF- or TDF-based regimens, the regimens were generally well-tolerated through a median of 143 weeks of exposure and follow-up. Significant improvements in long-term bone and renal safety were observed in women using TAF, and discontinuation due to AEs was uncommon (TAF 0 participants; TDF 1.6%, 2 participants). There was also less impact on markers of general and proximal tubular proteinuria in TAF users, and significantly lower changes in hip and spine BMD (even in women ≥ 50 years of age), indicating that the short-term safety advantages of TAF persist through at least 2 to 3 years of dosing.

The general AE profile was also consistent between treatment-naive women who took TAF and TDF, with some notable differences between the groups in the incidence of individuals events (Table 16) and SAEs (overall: TAF 19.5%, TDF 22.8%; treatment-related SAEs: 0.8% TAF, 3.1% TDF).
Table 16. Pooled Data from Genvoya Pivotal Studies: Adverse Events Reported for at Least 10% of Women Living with HIV in Either Treatment Group (Safety Analysis Set)

<table>
<thead>
<tr>
<th>Preferred Term; n (%)</th>
<th>TAF-Containing Regimen (N=133)</th>
<th>TDF-Containing Regimen (N=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea 24 (18.0%)</td>
<td>40 (31.5%)</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis 30 (22.6%)</td>
<td>32 (25.2%)</td>
<td></td>
</tr>
<tr>
<td>Headache 28 (21.1%)</td>
<td>28 (22.0%)</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection 26 (19.5%)</td>
<td>27 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea 29 (21.8%)</td>
<td>21 (16.5%)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia 23 (17.3%)</td>
<td>21 (16.5%)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection 18 (13.5%)</td>
<td>20 (15.7%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness 16 (12.0%)</td>
<td>19 (15.0%)</td>
<td></td>
</tr>
<tr>
<td>Back pain 16 (12.0%)</td>
<td>18 (14.2%)</td>
<td></td>
</tr>
<tr>
<td>Vaginal discharge 16 (12.0%)</td>
<td>14 (11.0%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting 15 (11.3%)</td>
<td>14 (11.0%)</td>
<td></td>
</tr>
<tr>
<td>Osteopenia 16 (12.0%)</td>
<td>10 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain 14 (10.5%)</td>
<td>4 (3.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Adverse events were coded using MedDRA 19.0. Preferred term was presented by decreasing order of the total frequency. Multiple AEs were counted only once per participant for each preferred term.

The data from the use of TAF- or TDF-based regimens in women confirm that Descovy has a significantly better renal and bone safety profile. And, because there are no meaningful differences in the pharmacokinetics in women who are HIV-positive or HIV-negative, these safety data support the use of TAF as an option for use in women without HIV.

Collectively with the pharmacokinetic data described above, this evidence-based bridge for safety data supports the use of Descovy for PrEP in women at risk of HIV and expands access to PrEP to women with preexisting bone or renal disease or risks of these diseases.

Clinical Studies of Descovy for PrEP in Women

Gilead is collaborating with external partners on studies of Descovy in cis-women in the US, Latin America, and Africa.

Several clinical trials are in planning that will evaluate the safety of Descovy in cis-women at risk of HIV.
5.3. Extrapolation to Adolescents

5.3.1. Data Strategy for Adolescents

Truvada is indicated for use in combination with safer sex practices for HIV PrEP to reduce the risk of sexually acquired HIV in at risk adults and adolescents weighing at least 35 kg \{Gilead Sciences Inc. 2018, TRUVADA 2018b\}. As with the approval for Truvada for PrEP, the extrapolation of PrEP efficacy data for Descovy (in this case, from the DISCOVER study) to an adolescent population was made in consultation with the FDA. Of note, Descovy (in combination with third agents) and the FTC/TAF-containing combination products Genvoya, Odefsey, and Biktarvy have been approved for the treatment of HIV in adolescents based upon a well-established understanding of the pharmacokinetics in adolescents and adults. A pharmacokinetic-based approach was thus implemented to extrapolate Descovy efficacy for PrEP from adults to adolescents. This bridging pathway is consistent with current FDA guidance for PrEP \{U. S. Department of Health & Human Services (DHHS) 2019\} and is considered appropriate because the acquisition of HIV infection and antiviral drug effects are sufficiently similar in adult and adolescent populations.

The specific data to support the bridge for the efficacy and safety of Descovy for PrEP to adolescents are briefly summarized below. Details for the relevant efficacy and safety assessments are provided in Sections 5.3.2 and 5.3.3, respectively

Efficacy

FTC, TAF and PBMC-associated TFV-DP pharmacokinetics for Descovy are comparable between HIV-infected adolescents (weighing at least 35 kg) and HIV-infected adults; the pharmacokinetics of these analytes for Descovy are comparable irrespective of HIV infection status as outlined in Figure 17 (Section 5.3.2) \{Custodio 2015, Emtriva 2016, Lutz 2018b\}. These data demonstrate that the efficacy of Descovy for PrEP can be extrapolated from participants in the DISCOVER study to adolescents at risk of HIV \{Appendix 9.4.2\}.

Additional supportive data are provided to show that Truvada has comparable PrEP efficacy in adolescents (weighing at least 35 kg) and adults.

Safety

FTC, TAF and TFV-DP pharmacokinetics within Descovy are comparable irrespective of HIV infection \{Appendix 9.4.2\}; therefore, the long-term safety of the FTC- and TAF-containing product Genvoya in adolescents with HIV supports the safety of Descovy for PrEP in adolescents at risk of HIV as described in Section 5.3.3.
5.3.2. Efficacy Extrapolation for Adolescents

Summary analyses of pharmacokinetic data from adolescents weighing at least 35 kg compared with adults that demonstrate comparable exposures of FTC and TAF and PBMC-associated TFV-DP are presented in Table 17, Table 18, and Table 19, respectively.

Plasma exposures of FTC were similar (90% CIs for FTC AUC\textsubscript{\texttau}, C\textsubscript{\textmax}, and C\textsubscript{\texttau} were within the equivalence boundary of 70% to 143%) between adolescents and adults with HIV who received FTC/TAF (as a component of Genvoya 150/150/200/10 mg) (Table 17). FTC exposures in adolescents were also within the range (fourth quartile [Q4]) of those observed in adults at risk of HIV in the DISCOVER trial, as well as those achieved historically with Truvada {Gilead Sciences Inc. 2018} (Appendix Table 10). Compared to adults with HIV, TAF AUC\textsubscript{\texttau} was similar (90% CI was within 70% to 143%) in adolescents and adults; whereas C\textsubscript{\textmax} of TAF was 50% lower in adolescents (Table 18). Considering the lack of exposure-response (safety/efficacy) relationship for TAF and in light of comparable TFV-DP concentrations in adolescents or adults with HIV taking F/TAF-containing regimens for treatment or adults taking Descovy for PrEP, this reduction in C\textsubscript{\textmax} was not deemed clinically meaningful (Appendix Table 11).

Furthermore, as expected based on the established pharmacokinetics of TAF, TFV-DP concentrations (Table 19) in adolescents taking Genvoya were higher than those achieved in adults in DISCOVER taking Truvada, an approved product for HIV prevention in adolescents.
### Table 17. Pooled Data: Summary and Statistical Comparison of FTC Plasma Pharmacokinetic Parameters in Adolescents Versus Adults Treated with Genvoya (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>FTC PK Parameter</th>
<th>Mean (%CV) (Q1, Q3)</th>
<th>% GLSM Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adolescents (N = 24)</td>
<td>Adults (N = 19)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;τ&lt;/sub&gt; (h•ng/mL)</td>
<td>14,424.4 (23.9) (12221.6, 17122.8)</td>
<td>11,714.1 (16.6) (10225.6, 12627.3)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>2265.0 (22.5) (1975.0, 2560.0)</td>
<td>2056.3 (20.2) (1860.0, 2363.7)</td>
</tr>
<tr>
<td>C&lt;sub&gt;τ&lt;/sub&gt; (ng/mL)</td>
<td>102.4 (38.9)&lt;sup&gt;a&lt;/sup&gt; (73.0, 128.0)</td>
<td>95.2 (46.7) (71.8, 94.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup> n = 23

The estimates and 90% CI were from an ANOVA model.

PK parameters for the adolescents (test group) were from adolescents with HIV.

PK parameters for adults (reference group) were from the adults with HIV who participated in a PK substudy.

One participant had missing values for C<sub>τ</sub>.

### Table 18. Pooled Data: Summary and Statistical Comparison of TAF Plasma Pharmacokinetic Parameters in Adolescents Versus Adults Treated with Genvoya (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>TAF Pharmacokinetic Parameter</th>
<th>Mean (%CV) (Q1, Q3)</th>
<th>% GLSM Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adolescents&lt;sup&gt;a&lt;/sup&gt; (N = 46)</td>
<td>Adults&lt;sup&gt;b&lt;/sup&gt; (N = 539)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;τ&lt;/sub&gt; (h•ng/mL)</td>
<td>195.3 (48.2) (108.8, 270.3)</td>
<td>206.4 (71.8) (140.5, 230.3)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>92.3 (68.2) (43.5, 120.0)</td>
<td>162.2 (51.1) (115.8, 195.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pharmacokinetic parameters for adolescents were population pharmacokinetic parameters from Cohort 1 participants in Study GS-US-292-0106.

<sup>b</sup> Pharmacokinetic parameters for adult population were from population pharmacokinetic parameters.

The estimates and 90% CI were from an ANOVA model.
Table 19. Pooled Data: Summary of Steady-state TFV-DP C_{tau} in Adolescents with HIV and Adults with HIV Treated with FTC/TAF-Containing Product/Regimen and in the DISCOVER Study (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>TFV-DP Pharmacokinetic Parameters</th>
<th>Adolescents</th>
<th>Adults</th>
<th>DISCOVER</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{tau} (fmol/million cells)</td>
<td>212.7 (56.5, 426.0)</td>
<td>270.6 (122.8, 593.7)</td>
<td>63.1 (32.4, 118.3)</td>
</tr>
</tbody>
</table>

Pharmacokinetic data (Appendix 9.4.2) demonstrate that the exposures of the FTC, TAF and TFV-DP are comparable between adolescents and adults with HIV, and between adults with and without HIV infection, demonstrating that HIV infection status does not impact the pharmacokinetics of these analytes, consistent with previous analyses {Custodio 2015, Emtriva 2016, Lutz 2018b}. Thus, the pharmacokinetics and clinical effects of FTC, TAF, and PBMC-associated TFV-DP in adults receiving Descovy for PrEP in the DISCOVER study and adolescents at risk of HIV infection are expected to be similar. Therefore, results of the DISCOVER study, which was conducted in adults are applicable to adolescents at risk of HIV infection.

5.3.3. Safety of Descovy in Adolescents

Descovy is approved for the treatment of adolescents with HIV for use in combination with third agents or as part of combination products. As such, the safety of these products has been demonstrated in multiple clinical studies. As shown in Section 5.3.2, exposures of FTC and TAF in adolescents with HIV weighing at least 35 kg were comparable to adults with HIV who received FTC/TAF-containing products {DESCOVY 2018, DESCOVY® 2017, Genvoya 2018b, GENVOYA® 2019}. The pharmacokinetics of the components of Descovy are not altered by HIV infection, as evidenced by comparable FTC and TAF exposures in adults with and without HIV infection (Appendix 9.4.2), demonstrating that HIV-infection status had no clinically meaningful influence on the exposures of these agents. As such, the safety profile of Descovy in adolescents with HIV is relevant to the expected profile in adolescents at risk of HIV infection.

The information below presents the safety findings for Descovy characterized in 50 adolescents with HIV receiving the FTC/TAF-containing fixed-dose combination product Genvoya for 48 weeks in the open-label Study GS-US-292-0106. The mean age in the study was 15 years; (range: 12 to 17 years). Approximately half (56%) of study participants were female. To meet eligibility, all participants were at least 35 kg in body weight.
Results from Study GS-US-292-0106 support that the safety profile of the use of FTC/TAF (ie, Descovy) in adolescents is favorable, as demonstrated by high tolerability, low incidence of study drug-related SAEs, and absence of AEs leading to study drug discontinuation. The majority of AEs and laboratory abnormalities reported were Grade 1 or 2 in severity. No new safety issues were identified in the adolescent safety population.

There were no renal and bone safety concerns for adolescents identified in Study GS-US-292-0106. There were no AEs of proximal renal tubulopathy (including Fanconi syndrome). One renal SAE was reported (urinary retention in a participant with a history of urinary retention, considered unrelated to study drug by the investigator). Fractures were reported for 2 participants; Grade 1 hand fracture in 1 participant, and Grade 3 radius fracture and ulnar fracture in 1 participant. No fracture was considered by the investigator to be related to study drug.

Changes from baseline in serum creatinine and eGFR by Schwartz formula (median: 0.07 mg/dL and −12.2 mL/min/1.73 m², respectively; Table 20) at Week 48 were consistent with the known inhibitory effect of cobicistat (COBI) on renal tubular secretion of creatinine, and are not considered reflective of changes in actual glomerular filtration. The changes in serum creatinine and eGFR were seen as early as Week 1 and subsequently stabilized and were nonprogressive. Decreases from baseline were observed in proteinuria markers (assessed by UPCR) and urine beta-2-microglobulin to creatinine ratio (β2M:Cr).

Descovy is not expected to have an impact on the rate of bone growth or bone mineralization in adolescents at risk for HIV, as demonstrated by the findings in Study GS-US-292-0106. In Study GS-US-292-0106, mean increases from baseline were seen in spine and total body less head (TBLH) BMD (Table 20). Three participants (6.4%) had ≥ 4% decrease from baseline in spine BMD during the study, one of whom shifted from BMD status within the expected range for age to low BMD status (BMD Z-score ≤ −2.0; {The International Society for Clinical Densitometry (ISCD) 2013}). No participant had a decrease of ≥ 4% in TBLH BMD. Because the study population was shorter than average for age (the median Z-score for height at baseline was −0.75), adjustment of BMD Z-scores is critical for interpretation of these data, as noted in the official position of the International Society for Clinical Densitometry on DXA evaluation in children and adolescents {Bianchi 2010}. Height-age BMD Z-scores did not change notably from baseline at Weeks 24 or 48, indicating that participants mineralized bone at rates consistent with those of the reference population.
Table 20. Measures of Renal and Bone Safety at Week 48 (Safety Analysis Set from Study GS-US-292-0106)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal AEs; n (%)</td>
<td>2 (4.0%)</td>
</tr>
<tr>
<td>Dipstick proteinuria; n (%)</td>
<td>19 (38.0%)</td>
</tr>
<tr>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Δ Serum Creatinine (mg/dL)</td>
<td>0.07</td>
</tr>
<tr>
<td>Δ eGFR by Schwartz formula (mL/min/1.73 m²)</td>
<td>−12.2</td>
</tr>
<tr>
<td>% Δ UPCR</td>
<td>−26.98</td>
</tr>
<tr>
<td>% Δ RBP:Cr</td>
<td>−21.57</td>
</tr>
<tr>
<td>% Δ β2M:Cr</td>
<td>−29.4</td>
</tr>
<tr>
<td>% Δ Spine BMD</td>
<td>3.261</td>
</tr>
<tr>
<td>% Δ TBLH BMD</td>
<td>0.931</td>
</tr>
</tbody>
</table>

Renal AEs were defined using the Renal and Urinary Disorders SOC.

5.4. Conclusions on Use of Descovy in Cis-Women and Adolescents

The use of PrEP as part of an effective HIV prevention strategy in at risk women and young persons is recommended in the CDC, American College of Obstetricians and Gynecologists (ACOG), and US Preventive Services Task Force (USPSTF) clinical recommendation guidelines {American College of Obstetricians and Gynecologists (ACOG) 2017, Center for Disease Control and Prevention (CDC) 2018b, Force 2019}. These populations are disproportionally represented among newly HIV-infected persons. According to recent CDC estimates, women made up 19% of new HIV infections in the US in 2017, with most (86%) infections occurring through heterosexual contact {Center for Disease Control and Prevention (CDC) 2017}. Youth made up a large portion of new HIV infections in the US (approximately 21% per CDC estimates), predominantly through sexual contact (99% and 86% of new HIV infections among young men and women, respectively) {Center for Disease Control and Prevention (CDC) 2017}. Globally, women made up 49% of the approximately 37 million people living with HIV/AIDS in 2017, and 1.8 million children under 15 years of age were estimated to be infected {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018}.

Cis-women may not be able to negotiate with their sex partners the use of known behavioral interventions that reduce sexual HIV risk (eg, mutual monogamy and condom use), and women may be disproportionately affected by structural violence (including intimate partner violence) discrimination, mental health disorders, poverty, and lack of access to education and healthcare. Adolescents and emerging adults are particularly vulnerable, as policy and legal barriers related to age of consent may prevent access to reproductive health services, including HIV and STI testing, and harm reduction services {World Health Organization (WHO) 2019}. Youth living with HIV are the least likely age group to be linked into HIV treatment, which can adversely affect their own individual health as well as increase the chance of forward transmission to their
partners {Pettifor 2015}. Given their potential vulnerability, it is important to expeditiously provide equal access to Descovy for PrEP to these populations.

Truvada, the only approved antiviral product for HIV PrEP, has comparable efficacy in men, women and adolescents. Descovy delivers more rapid, higher, sustained TFV-DP concentrations in PBMCs and higher TFV-DP concentrations in cervicovaginal tissue among cis-women relative to Truvada. The DISCOVER study data convincingly demonstrate that Descovy is comparable to Truvada in efficacy and superior to Truvada in bone and renal safety among men and TGW. Women have an increased lifetime risk of osteoporosis relative to men, and may therefore be disproportionately affected by TDF-mediated BMD loss. Adolescents and emerging adults continue to build to peak bone mass until approximately age 35 years. This bone-building process would be adversely impacted by TDF-mediated BMD loss. Descovy therefore offers a promising alternative to Truvada for PrEP in cis-women and adolescents.

The pharmacokinetics of the 2 individual drugs contained in Descovy have been comprehensively characterized across several clinical development programs of FTC/TAF-containing products (eg, Descovy, Genvoya, Biktarvy, Odefsey). These analyses have shown that the pharmacokinetics of FTC, TAF, and TFV-DP are not affected by demographic factors, including biologic sex at birth, current gender identity, sexual orientation, HIV infection, or age. As such, pharmacokinetic results across clinical programs in men, women and adolescents, including pharmacokinetic data generated in the DISCOVER population, form the basis for extrapolation of DISCOVER study efficacy data to cis-women and adolescents.

The pharmacokinetic extrapolations are supported by available efficacy data with Truvada that demonstrate comparable effectiveness efficacy in men, women, and adolescents for HIV prevention {Gilead Sciences Inc. 2018}. Pharmacokinetic data in female volunteers demonstrate that there are higher concentrations of TFV-DP in cervicovaginal tissues with Descovy as compared with Truvada.

From a safety perspective, clinical data with FTC+TAF from several large clinical development programs in chronic HIV treatment (eg, Genvoya, Odefsey, Biktarvy) in men, women, and adolescents form the basis for the characterization of Descovy safety. Descovy for PrEP particularly offers potential benefits over Truvada for younger individuals who are still mineralizing bone, those with risk factors for osteoporotic disease, and those at risk of renal disease. The safety benefits of Descovy over Truvada are also important for those who may use a PrEP regimen longer term as the relative safety advantages increase over time with clearer distinctions become apparent for both renal and bone clinical events through 96 to 144 weeks in people living with HIV.

Finally, results from clinical studies may be augmented by real-life experience of over 202,538 person-years of experience in cis-women with FTC/TAF-containing products in the postmarketing setting for HIV treatment and HBV treatment in the US.
Taken together, there is substantial evidence from nonclinical, pharmacokinetic, pharmacodynamic, and clinical efficacy and safety evaluations to support the use of Descovy for PrEP in cis-women and adolescent populations. As the pharmacokinetics of the components of Descovy are comparable irrespective of demographic factors including biologic sex, HIV infection status, or age, the proposed indication for Descovy for PrEP is purposefully inclusive of all adults and adolescents weighing at least 35 kg at sexual risk of acquiring HIV. The availability of Descovy for PrEP to all individuals at sexual risk of acquiring HIV will increase choices and provide a safer option for the prevention of HIV infection for men, women, and adolescents, and will contribute to the goal of preventing HIV among those who are at risk.
6. RISK MANAGEMENT

Effective mitigation of the potential risks of PrEP will be achieved through detailed prescriber and user instructions in the Descovy prescribing information and Medication Guide, reference to independent, scientifically rigorous clinical guidelines, and multiple outreach efforts following the approval of Descovy for PrEP to continue clinician and user education. As detailed throughout this document, since approval in 2012 of Truvada for PrEP, the HIV prevention landscape has changed dramatically. The rapid uptake of PrEP combined with the publication of clinical guidelines and educational efforts by both Gilead and independent clinical organizations has contributed to greater understanding of the critical link between efficacy and adherence and dissemination of knowledge of safe PrEP use among healthcare providers, PrEP users, and public health communities.

In addition to the data from the DISCOVER study, cumulative evidence indicates that the original concerns of nonadherence, seroconversion, and resistance development to the components of Truvada when used for PrEP are not occurring at a frequency that was originally anticipated in 2012 {Gibas 2019, McCormack 2017, Molina 2017b}. Additionally, postmarketing PrEP studies and data from real-world cohorts corroborate the increased adherence and concomitant decline in HIV seroconversions and low rates of resistance development {Baeten 2018, Gibson 2016, Marcus 2016}.

There is now a large body of educational material and independent clinical, academic, and public health guidelines in the public domain informing healthcare providers and PrEP users about the appropriate use of PrEP, including the importance of adherence to a daily dosing schedule, appropriate screening and monitoring of HIV status to avoid drug resistance, and the need for a comprehensive prevention plan to reduce sexual risk of HIV acquisition {Azar 2019}. Leading US and international guidelines, including CDC/Department of Health and Human Services (DHHS), IAS-USA, and World Health Organization (WHO), provide guidance on the safe use of PrEP, including important messages regarding patient counseling, adherence, monitoring, and the implementation of PrEP in clinical practice {Center for Disease Control and Prevention (CDC) 2018a, Center for Disease Control and Prevention (CDC) 2018b, Saag 2018, World Health Organization (WHO) 2012, World Health Organization (WHO) 2016}. The USPSTF, which is widely referenced by primary care clinicians, provides risk mitigation measures and links to additional guidance and recently issued an “A” recommendation for the use of Truvada for PrEP {Force 2019}.

In recognition of the successful educational efforts and the evolving HIV prevention landscape, the 2012 Truvada for PrEP Risk Evaluation Mitigation Strategy is considered complete and has now been removed.

Gilead will also continue its long-standing commitment to further education and awareness of the appropriate use of PrEP among healthcare providers. The following communications are planned to inform healthcare providers about the Descovy for PrEP indication once approved and point them to education and educational resources to support their product knowledge.
• Approval healthcare provider email announcement to 50,000 active PrEP healthcare providers/prescribers of PrEP including a link to a branded healthcare provider website to educate on the new indication and prescribing information, including important messages regarding patient counseling, adherence, monitoring.

• Sales representative approval announcement to 7,700+ healthcare providers containing an introduction to Descovy for PrEP and a link to a branded healthcare provider website.

• Direct mail packets to 15,000 healthcare providers to be sent in the first two weeks post launch. Packets will contain an announcement letter with clinical and product overviews.

• Live promotional speaker programs across the US post approval. The live programs will average 50 to 75 attendees and will be held in 27 cities across the US. The content will be label-consistent data from the DISCOVER study.

From 2012 to 2018, Gilead Medical Affairs provided funding support for 51 independent medical education programs focused on comprehensive HIV prevention education. At least 580,000 healthcare providers have been reached. For 2019, Gilead Medical Affairs has targeted 12 programs for funding that are anticipated to reach approximately 39,000 healthcare providers and which are focused on clinicians serving PrEP users with the higher unmet medical need.

In 2020 and beyond, Gilead will continue its long-standing commitment to further education and awareness of the appropriate use of PrEP among healthcare providers and the broader communities through the provision of independent medical education programs covering comprehensive HIV prevention. Program proposals that include the following topics will be preferentially funded: basics of HIV screening and testing, sexual health discussions in the clinic; HIV risk evaluation and assessment for PrEP; comprehensive HIV prevention services (including PrEP) for multiple types of healthcare providers; and healthcare access disparities in the provision of HIV prevention services. Grants-based educational programs are prioritized for funding if they target these healthcare provider segments: addiction medicine, primary care, LGBT healthcare, obstetrics/gynecology, pharmacy, public health, and student health, as well as healthcare providers working with underserved populations (black and Latino MSM, black women, TGW, and Native Americans). Likewise, educational programs will be preferentially funded that target healthcare providers in high-prevalence areas such as mid-to-large cities in the southern US and innovative sites for clinical HIV prevention services, including pharmacy-based settings, public health departments and student health centers. Program decisions for Gilead-supported independent medical education programs for 2020 will be determined in October 2019.

The proposed prescribing information and Medication Guide, extensive external resources and clinical guidelines, and Gilead’s ongoing commitment to clinician and user education will ensure responsible prescribing and management of PrEP by the healthcare community, in turn ensuring adherence to maximize efficacy and minimize the chance for drug resistance.
7. OVERALL CONCLUSIONS

The clinical advantages of Descovy are based on the pharmacokinetic characteristics of TAF. The DISCOVER study demonstrated the noninferiority of Descovy to Truvada in the prevention of HIV infection among men and TGW who have sex with men. Based on the findings from DISCOVER, extensive published clinical trial data, and a pharmacokinetic bridge for cis-women and adolescents, Gilead proposes a new Descovy for PrEP indication in all adults and adolescents at risk of HIV infection.
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Tao L, McCallister S, Smith L, Mera R, Magnuson D. HIV Infection and FTC/TDF in Dried Blood Spot: A Pooled Analysis of Global Studies [Poster #0986]. Conference on Retroviruses and Opportunistic Infections (CROI); 2019 04-07 March; Seattle, WA.


TRUVADA, Gilead Sciences Limited. TRUVADA 200mg/245mg film-coated tablets. Summary of Product Characteristics (SmPC). Date of revision September 2018. 2018a:

TRUVADA, Gilead Sciences Ltd. TRUVADA 200 mg/245 mg film-coated tablets. Summary of Product Characteristics (SmPC). London, United Kingdom. Revised: December. 2018b:


9. APPENDICES
9.1. **Assessment of Adherence Based on Dried Blood Spot Testing**

Exposure is defined as tenofovir diphosphate (TFV-DP) concentration inside red blood cells for each study drug group (F/TAF and F/TDF) as assessed by DBS concentration. Concentrations of TFV-DP in DBS assessments reflect cumulative exposure to study drug prior to the sampling time (dosing over a 2- to 3-month period based on a half-life of approximately 20 days for F/TAF and 17 days for F/TDF {Castillo-Mancilla 2013} {Yager 2019b}). Thus, as DBS concentration reflects long-term exposure to study drug, it serves as an objective measure of long-term adherence to study drug, and is less affected by potential variability in daily drug administration (ie, missing a dose or doses, varying the time of day of drug administration).

Previous analyses of data from a 72-week open-label cohort study {Grant 2014a} of men and TGW who have sex with men in previously enrolled PrEP trials (ATN-082, iPrEx, and US Safety Study) have shown that F/TDF PrEP efficacy is associated with TFV-DP concentrations in DBS, and that optimal efficacy may be achieved with concentrations consistent with at least 4 doses per week (Appendix Table 1). These results are consistent with previous analyses of TFV-DP concentrations in PBMCs {Anderson 2012d}.

### Appendix Table 1. Estimated Dose and F/TDF PrEP Protection Associated with DBS Concentration

<table>
<thead>
<tr>
<th>DBS Concentration (fmol/punch)</th>
<th>&lt;LLQ</th>
<th>LLQ-349</th>
<th>350-699</th>
<th>700-1249</th>
<th>≥1250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate dose (tablets/week)</td>
<td>None</td>
<td>&lt;2</td>
<td>2–3</td>
<td>4–6</td>
<td>7</td>
</tr>
<tr>
<td>Follow-up (% of visits)</td>
<td>25%</td>
<td>26%</td>
<td>12%</td>
<td>21%</td>
<td>12%</td>
</tr>
<tr>
<td>HIV-1 infections (n)</td>
<td>18</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Person-years per infection</td>
<td>384</td>
<td>399</td>
<td>179</td>
<td>316</td>
<td>181</td>
</tr>
<tr>
<td>HIV-1 incidence (95% CI)</td>
<td>4.70 (2.99–7.76)</td>
<td>2.25 (1.19–4.79)</td>
<td>0.56 (0.00–2.50)</td>
<td>0.00 (0.00–0.61)</td>
<td>0.00 (0.00–1.06)</td>
</tr>
</tbody>
</table>

Source: Uptake of pre-exposure prophylaxis, sexual practices, and HIV-1 incidence in men and transgender women who have sex with men: a cohort study {Grant 2014a}.

A more recent pharmacokinetic study of TFV-DP in DBS using directly observed therapy (DOT) dosing of F/TDF (at daily dosing of 33%, 67%, or 100%) {Anderson 2018} has estimated TFV-DP DBS concentrations associated with variable dosing and is shown consistent with results from the open-label cohort study. The modeling of data from this study has shown that the fitted (estimated) median (twenty-fifth and seventy-fifth percentiles) TFV-DP DBS concentrations in men were 375 (316, 444); 774 (653, 917); and 1389 (1173, 1646) fmol per punch for 2, 4, and 7 doses per week respectively {Anderson 2018}.

A separate crossover pharmacokinetic study of TFV-DP in DBS based on DOT dosing of F/TAF (at daily dosing of 33%, 67%, or 100%) is currently ongoing. Available preliminary data from this ongoing study {Yager 2019b} (CROI abstract and presentation), and the previous F/TDF DOT study {Anderson 2018}, were used to develop the adherence bands for F/TAF based on DBS concentration. The observed twenty-fifth percentile, median, and seventy-fifth percentile from these sources are presented in Appendix Table 2.
Considering that F/TAF delivers a lower concentration of tenofovir in RBCs, and that using a 3-mm punch disk to quantify the TFV-DP levels in RBCs are approximately one-eighth the values established for F/TDF, two 7-mm punched disks (an increase of 10.89 fold in total sample disk area) were used to quantify TFV-DP DBS concentration for participants who receive F/TAF.

**Appendix Table 2. Reported Estimates of DBS Concentrations at Different DOT Dose Levels**

<table>
<thead>
<tr>
<th>Daily Dosing in DOT Study</th>
<th>Treatment</th>
<th>Q1</th>
<th>Median</th>
<th>Q3</th>
</tr>
</thead>
<tbody>
<tr>
<td>33%</td>
<td>F/TDF (fmol/Punch)</td>
<td>424</td>
<td>518</td>
<td>670</td>
</tr>
<tr>
<td></td>
<td>F/TAF (fmol/Punches) - Abstract</td>
<td>613</td>
<td>663</td>
<td>741</td>
</tr>
<tr>
<td></td>
<td>F/TAF (fmol/Punches) - Presentation</td>
<td>510</td>
<td>663</td>
<td>788</td>
</tr>
<tr>
<td>67%</td>
<td>F/TDF (fmol/Punch)</td>
<td>806</td>
<td>946</td>
<td>1174</td>
</tr>
<tr>
<td></td>
<td>F/TAF (fmol/Punches) - Abstract</td>
<td>991</td>
<td>1351</td>
<td>1586</td>
</tr>
<tr>
<td></td>
<td>F/TAF (fmol/Punches) - Presentation</td>
<td>1030</td>
<td>1422</td>
<td>1683</td>
</tr>
<tr>
<td>100%</td>
<td>F/TDF (fmol/Punch)</td>
<td>1315</td>
<td>1542</td>
<td>1796</td>
</tr>
<tr>
<td></td>
<td>F/TAF (fmol/Punches) - Abstract</td>
<td>1526</td>
<td>1928</td>
<td>2559</td>
</tr>
<tr>
<td></td>
<td>F/TAF (fmol/Punches) - Presentation</td>
<td>1909</td>
<td>2199</td>
<td>2518</td>
</tr>
</tbody>
</table>

Ref: For F/TDF: {Anderson 2018} and F/TAF: Abstract {Yager 2019b} and presentation

As expected (relative to TDF dose in F/TDF and DBS disk size), a shift up in the distribution of reported TFV-DP concentrations for F/TAF, compared with F/TDF, in Appendix Table 2 was observed; approximately 30% based on the Week 12 data (Period 1 of the crossover study) and approximately 35% based on the Weeks 12 and 24 data (Period 1 and 2 of the crossover study) were included in the analyses for the abstract and the presentation, respectively. The cutoffs for F/TAF adherence levels were estimated by adjusting the established DBS concentration for F/TDF adherence levels associated with HIV protection (or risk of acquiring infection) reported in {Grant 2014a} (Appendix Table 1). The proposed cutoffs, by either using a 30% increase based on Period 1 results (free of any potential impact of crossover design) or assuming dose proportionality and relying on Q1 for the 33% and 67% dosing levels, are presented in Appendix Table 3.

**Appendix Table 3. Adherence Level Definitions Based on DBS Concentration**

<table>
<thead>
<tr>
<th>Adherence Level (Daily Tablets/Week)</th>
<th>Low (&lt;2)</th>
<th>Medium (2-3)</th>
<th>High (≥4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/TDF (fmol/Punch)</td>
<td>&lt; 350</td>
<td>350 to &lt; 700</td>
<td>≥ 700</td>
</tr>
<tr>
<td>F/TAF (fmol/Punches)</td>
<td>&lt; 450</td>
<td>450 to &lt; 900</td>
<td>≥ 900</td>
</tr>
</tbody>
</table>
9.2. Bayesian Analysis of the DISCOVER Study Primary Efficacy Endpoint

In this analysis, the Jeffreys prior, a noninformative prior, was used as the prior distribution of the incidence rates. Let $\lambda_1, \lambda_2$ be the event rates, $d_1, d_2$ be the total follow-up time, and $e_1, e_2$ be the number of events for Descovy and Truvada, respectively.

Using an approach developed by Guo (Guo 2006), the posterior distribution of 2 Poisson incidence ratios is calculated by:

$$\lambda_1/\lambda_2 \sim \left(\frac{d_2(2e_1 + 1)}{d_1(2e_2 + 1)}\right) F_{2e_1+1,2e_2+1}$$

where $F_{2e_1+1,2e_2+1}$ is an F-distribution with $(2e_1 + 1, 2e_2 + 1)$ degrees of freedom.

Thus, the probability that Descovy is more efficacious than Truvada ($\lambda_1/\lambda_2 < 1$) is:

$$\text{Prob} \left( F_{2e_1+1,2e_2+1} < \frac{d_1(2e_2 + 1)}{d_2(2e_1 + 1)} \right) = \text{Prob} \left( F_{15,31} < \frac{4369.7 \times 31}{4386.2 \times 15} \right) = 0.956$$

Similarly, the probability that $\lambda_1/\lambda_2 < 1.62$ is 0.998.

The predicted median is:

$$\left(\frac{d_2(2e_1 + 1)}{d_1(2e_2 + 1)}\right) F_{0.5,2e_1+1,2e_2+1} = 0.47$$

And the 95% credible interval is calculated by:

$$\left(\frac{d_2(2e_1 + 1)}{d_1(2e_2 + 1)}\right)^{F_{0.025,2e_1+1,2e_2+1}} \left(\frac{d_2(2e_1 + 1)}{d_1(2e_2 + 1)}\right)^{F_{0.975,2e_1+1,2e_2+1}} = (0.18, 1.11).$$

where $F_{\alpha,2er+1,2e_2+1}$ is the $\alpha$-quantile of the F distribution.
9.3. Analyses of Nonclinical Models of PrEP

The use of antiviral agents for HIV PrEP is supported by a number of animal studies, which demonstrated that tenofovir-containing products provided protection against SIV and SHIV infection in nonhuman primates (Tsai 1995), (Garcia-Lerma 2009), (Van Rompay 1998, Van Rompay 2000, Van Rompay 2001), (Van Rompay 2008), (Otten 2000), (Massud 2016), (Massud 2018a, Massud 2018b), (Cong 2011, Garcia-Lerma 2010, Garcia-Lerma 2008, Radzio 2012, Tsegaye 2015), (CONRAD NIRC Study 8793-1702). A key study in macaques demonstrated that a dosing regimen of daily oral FTC and TDF (administered via oral gavage) prevented infection via rectal SIV exposure in the majority of animals and was associated with delayed infection and lower acute viremia in animals with breakthrough infections (Garcia-Lerma 2008). Additionally, the oral FTC and TDF combination offered complete protection against an FTC-resistant virus containing M184V in macaques, demonstrating that administration of both FTC and TDF is important in geographic areas with widespread access to antiretroviral drugs where drug-resistant viruses are frequently transmitted.

Prevention of SHIV acquisition by coadministration of FTC and TAF has been demonstrated in multiple studies using macaque models of HIV transmission (Massud 2018a, Massud 2016, Massud 2018c) (CONRAD NIRC Study 8793-1702). Results of these studies are summarized below and are consistent with the above-cited multiple earlier studies that demonstrated prevention of SHIV acquisition by FTC and TDF. Comparative studies of TAF or FTC alone showed only partial protection and low efficacy (Garcia-Lerma 2011, Massud 2019).

A series of nonhuman primate studies have been conducted to evaluate the use of FTC and TAF for pre- and post-exposure HIV prophylaxis or the use of elvitegravir (EVG), cobicistat (COBI), FTC, and TAF for HIV PrEP (Appendix Table 4). These nonclinical efficacy studies each support the use of oral FTC and TAF for PrEP of HIV infection.
Appendix Table 4. Summary of FTC+TAF Combination In Vivo Prophylaxis Efficacy in Nonhuman Primate Models

<table>
<thead>
<tr>
<th>Abbreviated Journal Article Title/Reference</th>
<th>Test System / Route of Viral Inoculation</th>
<th>Test Article / Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of Intermittent Prophylaxis with FTC and TAF against Rectal SHIV Transmission {Massud 2016} (PC-412-2055)</td>
<td>Rhesus macaques / Intrarectal</td>
<td>FTC, TAF/ PO</td>
</tr>
<tr>
<td>Oral F/TAF/ PrEP Prevents Vaginal SHIV Infection in Monkeys {Massud 2018a}</td>
<td>Pig-tailed macaques / Intravaginal</td>
<td>FTC, TAF/ PO</td>
</tr>
<tr>
<td>Post-exposure prophylaxis with single doses of combination EVG/COBI/F/TAF protect macaques against rectal SHIV infection {Massud 2018e}</td>
<td>Rhesus macaques / Intrarectal</td>
<td>EVG, COBI, FTC, TAF/ PO</td>
</tr>
<tr>
<td>Oral F/TAF Plus an INSTI in Macaque SHIV Model (CONRAD NIRC Study 8793-1702)</td>
<td>Rhesus macaques / Intravaginal</td>
<td>EVG, COBI, FTC, TAF/ PO</td>
</tr>
</tbody>
</table>

COBI = cobicistat; EVG = elvitegravir; F = emtricitabine; FTC = emtricitabine; INSTI = integrase strand-transfer inhibitor; PO = oral administration; SHIV = simian HIV; TAF = tenofovir alafenamide

9.3.1. Evaluation of Intermittent Prophylaxis with TAF and FTC Against Rectal SHIV Transmission

The US CDC conducted a study to determine whether oral administration of FTC+TAF in rhesus macaques prevents rectal infection with a chimeric SHIV {Massud 2016}. In the study, Massud et al administered weekly inoculations of intrarectal SHIV to 12 healthy rhesus macaques. Six of the animals were administered FTC (20 mg/kg) + TAF (1.5 mg/kg) by oral gavage and the remaining 6 animals were administered placebo (saline control). The dose for TAF were selected based on an initial pharmacokinetic study in macaques wherein a TAF dose of 1.5 mg/kg was shown to result in intracellular concentrations of the active moiety TFV-DP in PBMCs consistent with those seen with use of a TAF 25 mg dose in humans. FTC was dosed at 20 mg/kg based on a similar rationale, and consistent with the previous study with FTC+TDF in macaques. While the definitive correlate of protection against mucosal viral exposure has not been established, intracellular levels of TFV-DP have been consistently associated with both virologic suppression and with prophylaxis across a variety of human and animal studies {Abdool Karim 2010, Anderson 2012a, Anderson 2014, Baeten 2012, Castillo-Mancilla 2013, Garcia-Lerma 2008, Grant 2010c, Van Rompay 2012, Van Rompay 2001}.

Plasma and PBMC concentrations of FTC and TAF following the first challenge are summarized in Appendix Table 5. Consistent with their long intracellular half-lives in PBMCs, 2- to 4-fold accumulation of TFV-DP and FTC-TP were observed over the course of the study.
Appendix Table 5. Select Parent and Metabolite Levels (Plasma and PBMC) at 24 Hours Post-Challenge

<table>
<thead>
<tr>
<th>Description</th>
<th>Concentration (µM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1’</td>
</tr>
<tr>
<td>Plasma TFV</td>
<td>0.0211 ± 0.0070</td>
</tr>
<tr>
<td>Plasma FTC</td>
<td>0.615 ± 0.253</td>
</tr>
<tr>
<td>PBMC TFV-DP</td>
<td>1.97 ± 0.96</td>
</tr>
<tr>
<td>PBMC FTC-TP</td>
<td>6.09 ± 3.89</td>
</tr>
</tbody>
</table>

FTC = emtricitabine; FTC-TP = emtricitabine triphosphate; TFV = tenofovir; TFV-DP = tenofovir diphosphate

* Values are the mean ± standard deviation of n = 6 animals following oral administration of 1.5 mg/kg TAF and 20 mg/kg FTC 24 hours before and 2 hours after viral challenge.

In the study, none of the 6 macaques that were administered FTC+TAF became infected with SHIV, whereas all 6 of 6 macaques given placebo became infected (Appendix Table 6). Overall, the prophylactic efficacy and pharmacokinetic data demonstrate that orally administered FTC and TAF, at doses resulting in PBMC exposures that are consistent with those achieved in humans administered a dose of F/TAF 200/25 mg, effectively prevents SHIV infection.

Appendix Table 6. Treatment Arms and Results in F/TAF Rectal Challenge Study

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>Timing of Treatment</th>
<th>Infected</th>
<th>Protected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>Negative Control (saline)</td>
<td>0</td>
<td>Pre (-24hr) and Post (+2hr)</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>F/TAF</td>
<td>20/1.5</td>
<td>Pre (-24hr) and Post (+2hr)</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

F = emtricitabine; TAF = tenofovir alafenamide

9.3.2. Evaluation of Oral FTC+TAF Prophylaxis Against Vaginal SHIV Transmission

In addition to the study conducted in male macaques, the US CDC also conducted a study to determine whether oral FTC+TAF can prevent vaginal SHIV infection in female macaques to a degree similar to that of FTC+TDF {Massud 2018a, Massud 2018b}. In the study, Massud et al dosed female pigtail macaques with FTC (20 mg/kg) + TAF (1.5 mg/kg; n = 6) or placebo (n = 5) by oral gavage 24 hours before and 2 hours after once per week vaginal SHIV challenge for up to 16 weeks.

As with the Massud 2016 study, the FTC and TAF doses selected were considered clinically relevant because PBMC-associated TFV-DP levels in pigtailed macaques (Appendix Table 7) were in the range of those observed in humans in the single-dose clinical pharmacokinetic study. However, plasma TFV levels in these animals were approximately 3-fold higher than those observed in humans {Cottrell 2017}, suggesting variability between species in TAF metabolism. As observed in humans, plasma TFV levels with TAF 1.5 mg/kg were lower than those observed following TDF 20 mg/kg, whereas PBMC-associated TFV-DP levels with TAF 1.5 mg/kg were higher than those observed following TDF 20 mg/kg (Appendix Table 7). Concentrations of TFV-DP 24 hours after TAF 1.5 mg/kg were comparable between vaginal and rectal tissues.
(\(p = 0.25\)); this is different than the finding that TFV-DP concentrations following FTC (20 mg/kg) + TDF (22 mg/kg) administration to female pigtailed macaques were 40-fold lower in vaginal tissue than in rectal tissue {Radzio 2012}.

**Appendix Table 7. Massud 2018: Summary of TFV and TFV-DP Pharmacokinetic Parameters following a Single Dose of FTC+TAF in Female Pigtailed Macaques**

<table>
<thead>
<tr>
<th>Biomatrix and Analyte</th>
<th>Pharmacokinetic Parameter</th>
<th>FTC (20 mg/kg) + TAF (1.5 mg/kg) Median (Range) (N = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma TFV</td>
<td>(C_{\text{max}}) (ng/mL)</td>
<td>17 (9.0–35.8)</td>
</tr>
<tr>
<td></td>
<td>AUC(_{0-24}) (h•ng/mL)</td>
<td>150 (130–360.3)</td>
</tr>
<tr>
<td>PBMC TFV-DP</td>
<td>(C_{\text{max}}) (fmol/10(^6) cells)</td>
<td>154 (218.5–294.0)</td>
</tr>
<tr>
<td></td>
<td>AUC(_{0-24}) (h•ng/mL)</td>
<td>2001 (1458–4347)</td>
</tr>
<tr>
<td>Vaginal tissue TFV-DP</td>
<td>(C_{24h}) (fmol/mg)</td>
<td>9 (5–11)</td>
</tr>
<tr>
<td>Rectal tissue TFV-DP</td>
<td>(C_{24h}) (fmol/mg)</td>
<td>11 (7–19)</td>
</tr>
</tbody>
</table>

TFV = tenofovir; TFV-DP = tenofovir diphosphate
Source: {Massud 2018a, Massud 2018b}

All 5 untreated controls became infected after a median of 5 (range = 2 to 14) SHIV exposures. In contrast, 5 of the 6 FTC+TAF-treated animals remained uninfected after 16 virus challenges (\(p = 0.012\) log-rank test). Each of the 5 protected animals had detectable PBMC-associated TFV-DP and FTC-TP (median [range] over 16-week period = 238 [123 – 829] and 1837 [1255 - 2653] fmol/10\(^6\) cells, respectively) at the time of virus exposure. In contrast, the PrEP breakthrough animal only had detectable FTC-TP (median over 16-week period = 1499 fmol/10\(^6\) cells). These data are consistent with the efficacy of intermittent FTC+TAF for the prevention of male rectal SHIV transmission in rhesus macaques {Massud 2016}.

**9.3.3. Evaluation of Oral FTC+TAF Plus an Integrase Strand Transfer Inhibitor as Prophylaxis Against Vaginal SHIV Transmission**

In another study in female macaques, conducted at the University of Louisiana at Lafayette under the principal investigator Francois Villinger, CONRAD evaluated the efficacy of various FTC+TAF + an INSTI dosing regimens compared with an FTC+TDF dosing regimen equivalent to daily Truvada in humans in the prevention of vaginal SHIV infection in rhesus macaques (CONRAD NIRC Study 8793-1702). Female rhesus macaques were administered FTC+TAF+COBI-boosted EVG 2 hours before, 2 hours after, or 6 hours after viral challenge; FTC+TDF 24 hours before and 2 hours after viral challenge; or placebo. Following a single, high-dose vaginal SHIV challenge, all 4 placebo-treated animals were infected within 2 weeks, whereas 4 of 6 animals that were administered FTC+TDF were protected through 12 weeks post-challenge, and 4 of 5 animals that were administered FTC+TAF+EVG+COBI either 2 hours before or 2 hours after viral challenge were protected; 2 of 5 animals that received FTC+TAF+EVG+COBI 6 hours after viral challenge were protected.
9.4. Analyses of Clinical Pharmacology Data

9.4.1. Clinical Pharmacology Analyses Supporting Extrapolation of DISCOVER Data to Women

Comparisons of plasma exposures of FTC and TAF, and PBMC-associated TFV-DP from female and male volunteers in multiple-dose, Phase 1 studies following administration of FTC and TAF are provided below. These comparisons support extrapolation of efficacy data from the DISCOVER study. Appendix Table 8 summarizes the number of participant samples analyzed by analyte. Table 11, Table 12, and Table 13 (Section 5.2.2) summarize the pharmacokinetic parameters in women relative to men for FTC, TAF, and TFV-DP, respectively. Appendix Table 9 and Appendix Table 10 show a comparison of data from the pharmacokinetic parameters of FTC and TAF, respectively, in female volunteers (not HIV infected) relative to women with HIV-1 infection.

Mean FTC exposures (AUC$_\text{tau}$ and C$_\text{max}$) were similar between female volunteers and women with HIV-1; the GLSM ratios and 90% CIs for these pharmacokinetic parameters were within the equivalence boundary of 70% to 143% (Appendix Table 9). Emtricitabine C$_\text{tau}$ was ~35% lower in female volunteers than it was in women with HIV-1. This was not considered clinically relevant as a lower FTC C$_\text{tau}$ is not expected to have an impact on safety and FTC C$_\text{tau}$ in female volunteers and is similar to male volunteers.

Mean TAF exposures (AUC$_\text{tau}$ and C$_\text{max}$) were approximately 76% and 91% higher, respectively, in female volunteers relative to women with HIV-1 (Appendix Table 10). The higher TAF exposures observed in female volunteers were considered acceptable as no relationship between exposure and safety was identified for TAF in the Phase 3 studies of Genvoya, Descovy, or Biktarvy {Custodio 2016, Lutz 2018a}. Exposures of TAF in female volunteers were within the range of those for which safety has been established in the Genvoya, Descovy, and Biktarvy development programs {BIKTARVY® 2018a, BIKTARVY® 2018b, DESCOVY 2018, DESCOVY® 2017, GENVOYA 2018a, GENVOYA® 2018a}. These results are consistent with previous population pharmacokinetic analyses, which showed that HIV-1 infection status had no clinically relevant impact on TAF exposures.

Appendix Table 8. Sample Size by Analyte for Pharmacokinetic Analysis of FTC and TAF in Male and Female Volunteers and Women with HIV-1

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Female Volunteers$^a$</th>
<th>Male Volunteers$^a$</th>
<th>Women with HIV-1$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTC</td>
<td>91</td>
<td>142</td>
<td>30</td>
</tr>
<tr>
<td>TAF</td>
<td>138</td>
<td>161</td>
<td>169</td>
</tr>
</tbody>
</table>

$^a$ Intensive pharmacokinetic parameters from Phase 1 studies of Genvoya, Descovy, Biktarvy, and Vemlidy

$^b$ Population pharmacokinetic parameters from Phase 2 and 3 studies of Genvoya, Biktarvy, and Stribild
### Appendix Table 9. Pooled Data: Statistical Comparison of FTC Plasma Pharmacokinetic Parameters between Female Volunteers and Women with HIV-1 (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>FTC Pharmacokinetic Parameter</th>
<th>Mean (CV%) (Q1, Q3)</th>
<th>Women with HIV-1 (N = 30)</th>
<th>% GLSM Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female Volunteers (N = 91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{tau} (h•ng/mL)^a</td>
<td>12,099.6 (21.2) (10,349.7, 13,213.4)</td>
<td>14,414.2 (21.8) (12,133.1, 16,293.8)</td>
<td>83.99 (78.11, 90.31)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>2336.8 (21.5) (1940.0, 2620.0)</td>
<td>2277.7 (22.6) (1970.0, 2507.3)</td>
<td>102.50 (95.26, 110.30)</td>
</tr>
<tr>
<td>C_{tau} (ng/mL)^a</td>
<td>75.9 (39.3) (54.9, 84.8)</td>
<td>162.4 (187.8) (83.7, 121.8)</td>
<td>64.45 (55.52, 74.81)</td>
</tr>
</tbody>
</table>

The estimates and 90% CI were from an ANOVA model. Data from female volunteers were pooled from 9 multiple-dose, Phase 1 pharmacokinetic studies. Data from women with HIV-1 were pooled from 8 Phase 2 and Phase 3 studies.

a N = 28 women with HIV-1 for AUC_{tau} and C_{tau}

### Appendix Table 10. Pooled Data: Statistical Comparison of TAF Plasma Pharmacokinetic Parameters between Female Volunteers and Women with HIV-1 (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>TAF Pharmacokinetic Parameter</th>
<th>Mean (CV%) (Q1, Q3)</th>
<th>Women with HIV-1 (N = 169)</th>
<th>% GLSM Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female Volunteers (N = 138)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{tau} (h•ng/mL)^a</td>
<td>338.5 (34.9) (250.7, 406.7)</td>
<td>226.5 (132.1) (144.0, 211.3)</td>
<td>176.33 (161.26, 192.81)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>313.3 (65.9) (196.0, 383.0)</td>
<td>158.5 (50.7) (119.7, 183.0)</td>
<td>190.94 (173.10, 210.63)</td>
</tr>
</tbody>
</table>

The estimates and 90% CI were from an ANOVA model. Data from female volunteers were pooled from 11 multiple-dose, Phase 1 pharmacokinetic studies. Data from women with HIV-1 were pooled from 6 Phase 2 and Phase 3 studies.

a N = 133 female volunteers for AUC_{tau}

For comparison with the results in the DISCOVER study, trough concentrations of plasma FTC (C_{tau}) were equivalent following administration of Descovy and Truvada as assessed at Week 4 of the study (Appendix Table 11). Additionally, they were similar to historical data following administration of approved FTC-containing products, including Genvoya (GEN [E/C/F/TAF 150/150/200/10 mg]), Stribild® (STB [E/C/F/TDF 150/150/200/300 mg]), Biktarvy (BVY [B/F/TAF 50/200/25 mg]), Odefsey (ODE [F/R/TAF 200/25/25 mg]), and Descovy [F/TAF 200/25 mg]) {BIKTARVY® 2018a, BIKTARVY® 2018b, DESCOVY 2018, DESCOVY® 2017, Genvoya 2018b, GENVOYA® 2018b, Odefsey 2017, ODEFSEY® 2017, Stribild 2018a, Stribild 2018b}. 
Appendix Table 11. DISCOVER: Statistical Comparisons of FTC PK Parameters Following Administration of Descovy or Truvada (PK Cohort Analysis Set)

<table>
<thead>
<tr>
<th>PK Parameter[a]</th>
<th>Mean (CV%) (Q1, Q3)</th>
<th>GLSM Ratio% (90% CI) (Test/Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Descovy (Test) (N = 164)</td>
<td>Truvada (Reference) (N = 160)</td>
</tr>
<tr>
<td>FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{tau}}$ (ng/mL)</td>
<td>150.5 (201.0) (59.9, 100)</td>
<td>141.8 (206.8) (58.9, 101.1)</td>
</tr>
</tbody>
</table>

CI = confidence interval; CV% = percent coefficient of variation; F, FTC = emtricitabine; GLSM = geometric least-squares mean; Q1, Q3 = first quartile, third quartile; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

For each participant, a trough PK sample was collected at Week 4. Only trough samples (i.e., sampling time within a range of 20.0 to 28.0 hours, inclusive, after dosing time) were included for summary statistics.

Likewise in the DISCOVER study, consistent with historical data from multiple clinical programs using TAF-based FDC regimens for the treatment of HIV-1 infection, the mean PBMC-associated TFV-DP $C_{\text{tau}}$ was substantially (6.3-fold) higher following administration of Descovy compared with Truvada (Appendix Table 12). The range (first quartile, third quartile [Q1, Q3]) of PBMC-associated TFV-DP trough concentrations in this study were similar with those observed following administration of TAF-containing or TDF-containing regimens.

Appendix Table 12. DISCOVER: Statistical Comparisons of TFV-DP PK Parameters Following Administration of Descovy or Truvada (PK Cohort Analysis Set)

<table>
<thead>
<tr>
<th>PK Parameter[a]</th>
<th>Mean (CV%) (Q1, Q3)</th>
<th>GLSM Ratio% (90% CI) (Test/Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Descovy (Test) (N = 158)</td>
<td>Truvada (Test) (N = 151)</td>
</tr>
<tr>
<td>TFV-DP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{tau}}$ (fmol/million cells)</td>
<td>728.9 (156.8) (225.9, 711.1)</td>
<td>157.5 (234.2) (34.4, 105.3)</td>
</tr>
</tbody>
</table>

CI = confidence interval; CV% = percent coefficient of variation; DP = diphosphate; F, FTC = emtricitabine; GLSM = geometric least-squares mean; Q1, Q3 = first quartile, third quartile; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

For each participant, a trough PK sample was collected at Week 4. Only trough samples (i.e., sampling time within a range of 20.0 to 28.0 hours, inclusive, after dosing time) were included for summary statistics.
9.4.2. Clinical Pharmacology Analyses Supporting Extrapolation of DISCOVER Data to Adolescents

Comparisons of plasma exposures of FTC and TAF, and PBMC-associated TFV-DP from adolescents (weighing at least 35 kg) with HIV-1 and adults with HIV-1 following administration of FTC and TAF are provided in support of extrapolation of efficacy data from the DISCOVER study. Also provided are plasma exposure results for adult volunteers relative to adults with HIV-1. Appendix Table 13 and Appendix Table 14 summarize the number of participant samples analyzed by analyte.

Table 17, Table 18, and Table 19 (Section 5.3.2) summarize the pharmacokinetic parameters in adolescents relative to adults for FTC, TAF, and TFV-DP, respectively. Appendix Table 15, Appendix Table 16, and Appendix Table 17 provide a comparison of data from the key pharmacokinetic parameters of FTC, TAF, and TFV-DP, respectively, in adult volunteers (not HIV infected) relative to adults with HIV-1 infection.

Plasma FTC exposures were similar in adults with and without HIV infection (Appendix Table 15); the GLSM ratios and associated 90% CIs for FTC AUC$_{\text{tau}}$, C$_{\text{max}}$, and C$_{\text{tau}}$ were within the equivalence boundary of 70% to 143%. These results indicate that HIV disease status has no impact on FTC exposures. This result is consistent with historical FTC data {EMTRIVA. 2018, EMTRIVA® 2018}.

With respect to TAF, AUC$_{\text{tau}}$ and C$_{\text{max}}$ were 58% and 66% higher, respectively, in adult volunteers compared with adults with HIV-1 (Appendix Table 16). These mean increases in TAF exposures in adult volunteers were not considered clinically important as no relationship between exposure and safety was identified for TAF in the Phase 3 studies of Genvoya, Descovy, or Biktarvy (Genvoya m2.7.2, Section 3.3.2; {Custodio 2016, Lutz 2018a}). Further, TAF exposures in adult volunteers were within the range of those for which safety has been established in the Genvoya, Descovy, and Biktarvy development programs {BIKTARVY® 2018a, BIKTARVY® 2018b, DESCOVY 2018, DESCOVY® 2017, GENVOYA 2018a, GENVOYA® 2018a}.

These results are consistent with previous population PK analyses which showed that HIV infection status had no clinically relevant impact on TAF exposures.

Mean TFV-DP trough concentrations with TAF were similar in adult volunteers and adults with HIV-1, and were higher than those observed in adults receiving Truvada (Appendix Table 17). (Results from the DISCOVER study are also shown for comparison.)

Lastly, because the extrapolation of efficacy is based on plasma exposures following administration of FTC and TAF from combination products, the bioequivalence of FTC (200 mg) and TAF (25 mg) in Descovy versus Genvoya (E/C/F/TAF 150/150/200/10 mg) is demonstrated by the statistical comparison of plasma FTC and TAF in the primary pharmacokinetic parameters from a Gilead bioequivalence study (Appendix Table 18). The GLSM ratios and corresponding 90% CIs of AUC$_{\text{last}}$, AUC$_{\text{inf}}$, and C$_{\text{max}}$ for FTC and TAF were contained within the 80% to 125% boundary criteria specified for bioequivalence {DESCOVY 2018, DESCOVY® 2017, GENVOYA 2018a, GENVOYA® 2018a}. 
Appendix Table 13. Clinical Study Included in the Pharmacokinetic Analysis of FTC and TAF in Adolescents with HIV-1

<table>
<thead>
<tr>
<th>Study</th>
<th>Data Included</th>
<th>Product</th>
<th>Number of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-US-292-0106</td>
<td>Pharmacokinetics</td>
<td>Genvoya</td>
<td>48(^a)</td>
</tr>
</tbody>
</table>

\(^a\) Population Pharmacokinetic Analysis Set was used for pharmacokinetic analysis, which included 46 adolescents with HIV-1.

Appendix Table 14. Sample Sizes for Pharmacokinetic Data in Adolescents with HIV-1, Adults with HIV-1, and Adult Volunteers

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Adolescents with HIV-1</th>
<th>Adults with HIV-1 (Historic Control)</th>
<th>Adult Volunteers(^d)</th>
<th>Adults with HIV-1(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTC</td>
<td>24(^a)</td>
<td>19(^a)</td>
<td>233</td>
<td>155</td>
</tr>
<tr>
<td>TAF</td>
<td>46(^b)</td>
<td>539(^b)</td>
<td>299</td>
<td>1362</td>
</tr>
<tr>
<td>TFV-DP</td>
<td>8</td>
<td>569(^c)</td>
<td>55</td>
<td>569(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Intensive pharmacokinetic parameters
\(^b\) Population pharmacokinetic parameters
\(^c\) TFV-DP trough concentrations from Descovy+3rd agents or Truvada+3rd agents
\(^d\) Intensive pharmacokinetic parameters from Phase 1 studies of Genvoya, Descovy, Biktarvy, and Vemlidy.
\(^e\) Population pharmacokinetic parameters from Phase 2 and 3 studies of Genvoya, Biktarvy, and Stribild (pharmacokinetic parameters for pharmacokinetic and intensive pharmacokinetic parameters for FTC).

Appendix Table 15. Pooled Data: Summary and Statistical Comparisons of FTC Plasma Pharmacokinetic Parameters in Adult Volunteers Versus Adults with HIV-1 Treated with FTC− and TAF-Containing Products (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>FTC Pharmacokinetic Parameter</th>
<th>Mean (%CV) (Q1, Q3)</th>
<th>% GLSM Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult Volunteers (N = 233)</td>
<td>Adults with HIV-1 (N = 155)</td>
</tr>
<tr>
<td>AUC(_{\text{tau}}) (h•ng/mL)</td>
<td>11,149.9 (19.7) (9656.1, 12166.8)</td>
<td>12,437.9 (30.1)(^a) (10205.3, 14113.5)</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>2096.3 (23.6) (1750.0, 2380.0)</td>
<td>2040.8 (30.9) (1605.8, 2400.0)</td>
</tr>
<tr>
<td>C(_{\text{tau}}) (ng/mL)</td>
<td>77.3 (30.7) (61.1, 88.6)</td>
<td>113.8 (125.3)(^b) (75.9, 117.0)</td>
</tr>
</tbody>
</table>

\(^a\) N = 153
\(^b\) N = 151

The estimates and 90% CI were from an ANCOVA model.
Appendix Table 16. Pooled Data: Summary and Statistical Comparisons of TAF Plasma Pharmacokinetic Parameters in Adult Volunteers Versus Adults with HIV-1 Treated with TAF-Containing Products (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>TAF Pharmacokinetic Parameter</th>
<th>Mean (%CV) (Q1, Q3)</th>
<th>Adult Volunteers (N = 299)</th>
<th>Adults with HIV-1 (N = 1362)</th>
<th>% GLSM Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (h•ng/mL)</td>
<td>293.4 (38.9)a (211.4, 363.9)</td>
<td>185.8 (85.5) (129.4, 197.9)</td>
<td>157.90 (150.40, 165.78)</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>272.6 (65.3) (158.0, 342.0)</td>
<td>146.7 (50.2) (114.0, 165.5)</td>
<td>165.83 (157.85, 174.21)</td>
<td></td>
</tr>
</tbody>
</table>

a N = 293
The estimates and 90% CI were from an ANCOVA model.

Mean TFV-DP trough concentrations with TAF were similar in adult volunteers and adults with HIV-1, and were higher than those observed in adults receiving Truvada (Appendix Table 17). (Results from the DISCOVER study are also shown for comparison.)

Appendix Table 17. Pooled Data: Summary of TFV-DP Plasma Pharmacokinetic Parameters in Adult Volunteers and Adults with HIV-1 Treated with GEN (Pharmacokinetic Analysis Set)

<table>
<thead>
<tr>
<th>TFV-DP PK Parameter</th>
<th>Mean (%CV) (Q1, Q3)</th>
<th>DISCOVERa</th>
<th>Adult Volunteers</th>
<th>Adults with HIV-1d,e</th>
<th>F/TAF+3rd Agent (N = 304)f</th>
<th>F/TDF+3rd Agent (N = 265)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmin (fmol/million cells)</td>
<td>728.9 (156.8) (225.9, 711.1)</td>
<td>157.5 (234.2) (34.4, 105.3)</td>
<td>434.0 (108.7) (185.2, 536.7)</td>
<td>284.7 (92.1) (167.7, 317.6)</td>
<td>430.2 (114.1) (122.8, 593.7)</td>
<td>98.98 (139.0) (32.4, 118.3)</td>
</tr>
</tbody>
</table>

a Mean TFV-DP trough concentration was from blood samples collected at Week 4.
b Mean TFV-DP trough concentration was from blood samples collected at Week 4 from adult volunteers receiving B/F/TAF once daily.
c Mean TFV-DP trough concentration was from blood samples collected at Day 14 from adult volunteers receiving TAF once daily.
d Mean TFV-DP trough concentration was from blood samples collected at Week 4, Week 8, or Week 12 from adults following administration of F/TAF + third agents or F/TDF + third agents.
e Four and 6 participants in the F/TAF and F/TDF group, respectively, were excluded from PBMC analysis because the PBMC samples were out of the 61 days window of stability (ie, sample age ≥ 61 days).
f One participant received raltegravir as a third agent and was incorrectly enrolled into the F/TAF 10 mg stratum and received randomized study drug. This participant was excluded from this summary.

The GLSM ratios and corresponding 90% CIs of AUClast, AUCinf, and Cmax for FTC and TAF were contained within the 80% to 125% boundary criteria specified for bioequivalence {DESCOVY 2018, DESCOVY® 2017, Genvoya 2018b, GENVOYA® 2019}. 

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Appendix Table 18. Summary and Statistical Comparisons of FTC and TAF Pharmacokinetic Parameter Estimates Between Test and Reference Treatments (FTC, TAF, and All Pharmacokinetic Analysis Sets)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Descovy (Test)</th>
<th>Genvoya (Reference)</th>
<th>% GLSM Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean (%CV)</td>
<td>n</td>
<td>Mean (%CV)</td>
</tr>
<tr>
<td>----</td>
<td>---------------------</td>
<td>----</td>
<td>---------------------</td>
</tr>
<tr>
<td>TAF</td>
<td>116</td>
<td>374.0 (43.4)</td>
<td>116</td>
</tr>
<tr>
<td>AUC_last (h•ng/mL)</td>
<td>95</td>
<td>396.4 (42.6)</td>
<td>97</td>
</tr>
<tr>
<td>AUC_inf (h•ng/mL)</td>
<td>116</td>
<td>280.5 (62.9)</td>
<td>116</td>
</tr>
<tr>
<td>FTC</td>
<td>116</td>
<td>9423.9 (19.3)</td>
<td>116</td>
</tr>
<tr>
<td>AUC_last (h•ng/mL)</td>
<td>116</td>
<td>9654.6 (19.3)</td>
<td>116</td>
</tr>
<tr>
<td>AUC_inf (h•ng/mL)</td>
<td>116</td>
<td>1577.4 (26.8)</td>
<td>116</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>116</td>
<td>1577.4 (26.8)</td>
<td>116</td>
</tr>
</tbody>
</table>

The estimates and 90% CI were from an ANOVA model.