CLINICAL REVIEW AND SUMMARY CDTL

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

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Glossary

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

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

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

1. Executive Summary

1.1. Product Introduction

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

1.2. Conclusions on the Substantial Evidence of Effectiveness

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

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

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

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

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

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

the trial results.

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

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

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

Benefit-Risk Dimensions

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

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

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

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

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

1.4. Patient Experience Data

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

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

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

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

2. Therapeutic Context

2.1. Analysis of Condition

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

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

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

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

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

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

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

2.2. Analysis of Current Treatment Options

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

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

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

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

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

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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

3.2. Summary of Presubmission/Submission Regulatory Activity

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

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

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

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

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

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

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

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

The FDA also encouraged the Applicant to consider enrolling at-risk adolescents directly into its registrational trials (local regulations permitting) in order to collect adherence and clinical safety data in this population. However, because F/TDF was not approved for PrEP in adolescents at the time the pivotal trial was initiating and given that F/TDF would be used as the comparator arm, the Applicant opted to limit enrollment in its Phase 3 program to adults 18 years of age or older and rely upon extrapolation of adult efficacy data to support an indication in adolescents. This was agreed to in the Initial Pediatric Study Plan (iPSP), dated December 20, 2016 (see Section 8.8.3).

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

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

3.3. Foreign Regulatory Actions and Marketing History

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

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

4.1. Office of Scientific Investigations (OSI)

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

4.2. Product Quality

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

4.3. Clinical Microbiology

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

Clinical Virology

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

Nonclinical Virology

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

Rectal Challenge Studies

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

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

Vaginal Challenge Studies

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

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

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

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

4.4. Nonclinical Pharmacology/Toxicology

No new information was submitted.

4.5. Clinical Pharmacology

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

Background

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

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

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

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

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

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

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

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

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

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

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

2017}.

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

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

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

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

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

Study A15-137

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

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

Study Design

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

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

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

The following PK samples were collected:

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

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

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

Study Results

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

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

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

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

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

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

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

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

Office of Study Integrity and Surveillance

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

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

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

Study GS-US-412-2055

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

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

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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

Table 3: Listing of Clinical Trials

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

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

5.2. Review Strategy

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

6. Review of Relevant Individual Trials Used to Support Efficacy

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

6.1.1. Study Design

Overview and Objective

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

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

The primary objective of the trial was as follows:

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

Secondary objectives included:

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

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

Exploratory objectives included:

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

Trial Design

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

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

<u>Dose Selection</u>

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

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

Active Control and Noninferiority Margin

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

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

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

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

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

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

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

Eligibility Criteria

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

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

Assignment to Treatment and Blinding

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

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

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

Administrative Structure

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

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

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

Procedures and Schedule of Assessments

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

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

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

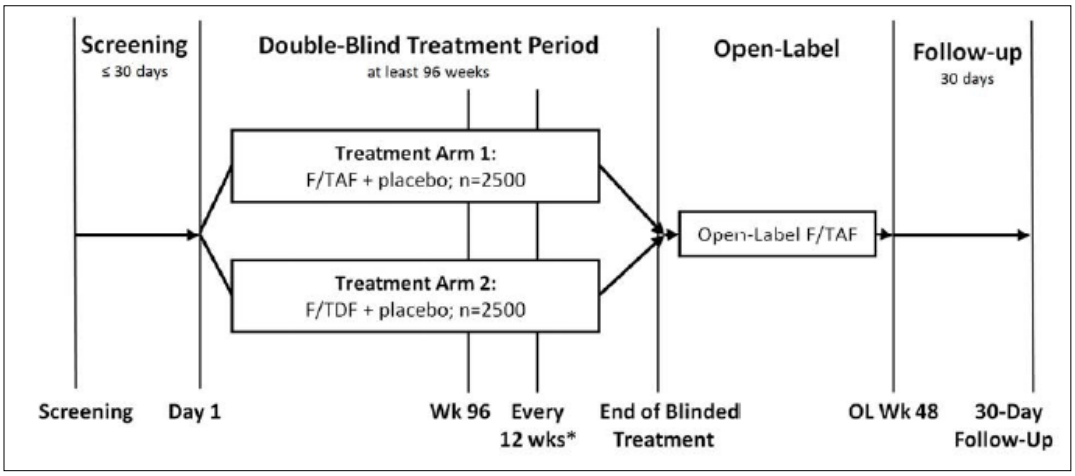
After screening, eligible subjects returned to clinic within 30 days for the Day 1 visit, during which eligibility was confirmed via local tests of 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab. Subjects were then randomized 1:1 to F/TAF or F/TDF and treated for 96 weeks. Subjects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

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

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

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

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



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

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

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

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

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

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

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

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

Concomitant and Rescue Medications

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

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

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

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

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

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

Treatment Compliance

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

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

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

Subject Discontinuation or Withdrawal

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

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

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

Study Endpoints

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

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

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

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

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

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

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

Statistical Analysis Plan

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

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

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

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

Protocol Amendments

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

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

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

6.1.2. Study Results

Compliance with Good Clinical Practices

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

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

Financial Disclosure

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

Patient Disposition

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

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

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

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

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

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

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

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

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

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

Protocol Violations/Deviations

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

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

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

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

Demographic Characteristics

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

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

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

Efficacy Results – Primary Endpoint

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

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

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

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

Sensitivity Analyses of the Primary Endpoint

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

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

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

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

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

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

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

Comparison of Observed HIV Infection Rate to External Sources

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

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

Characteristics of Subjects Infected with HIV-1

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

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

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

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

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

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

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

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

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

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

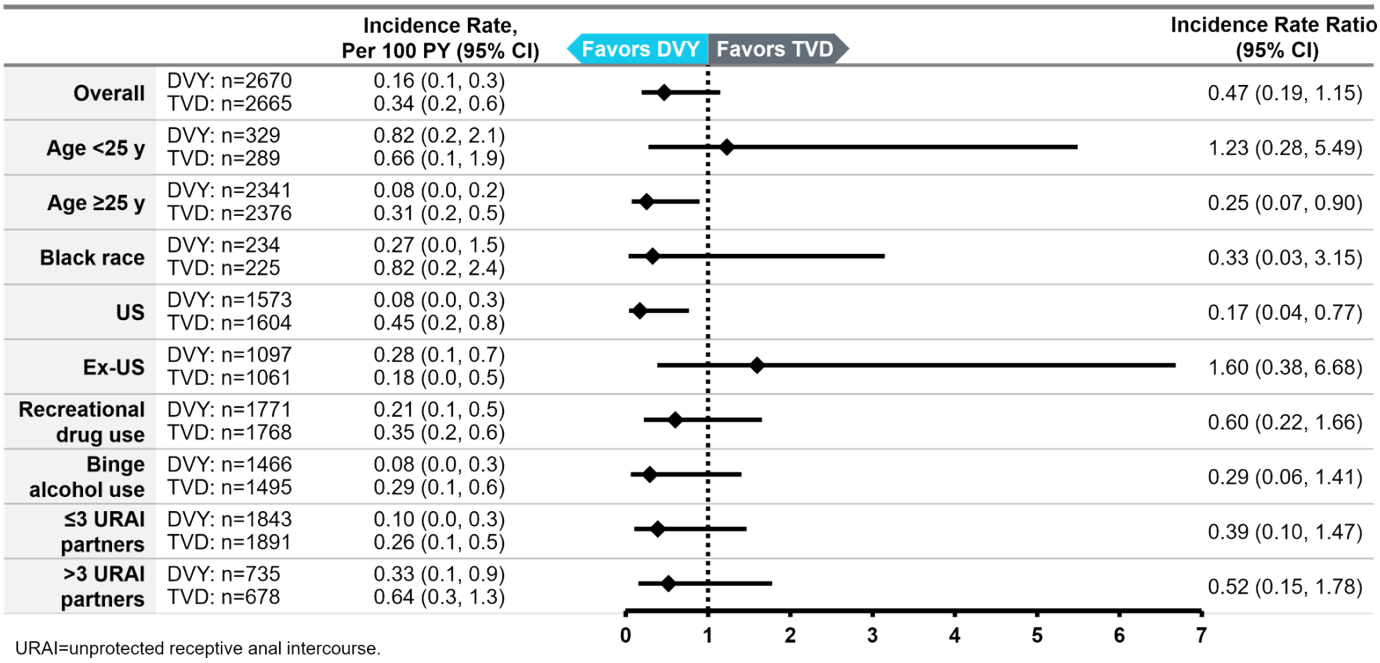
Subject ID	Age	Race	Hispanic Latino	Country	Circ	Prior PrEP	Day D/C Study Drug	Days to HIV+	# UIAI 90D	# URAI 90D	Recreational Drug Use	STIs During Trial	Adherence/ Comments
(b) (6)						(at B/L)						CT rectal Syphilis	
	25	White	No	UK	No	Yes (not at B/L)	209 (non-compliance)	228	3	13	Yes	GC rectal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

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

Subgroup Analyses of the Primary Endpoint

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

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



URAI=unprotected receptive anal intercourse.

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

Data Quality and Integrity

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

Efficacy Results – Secondary and other relevant endpoints

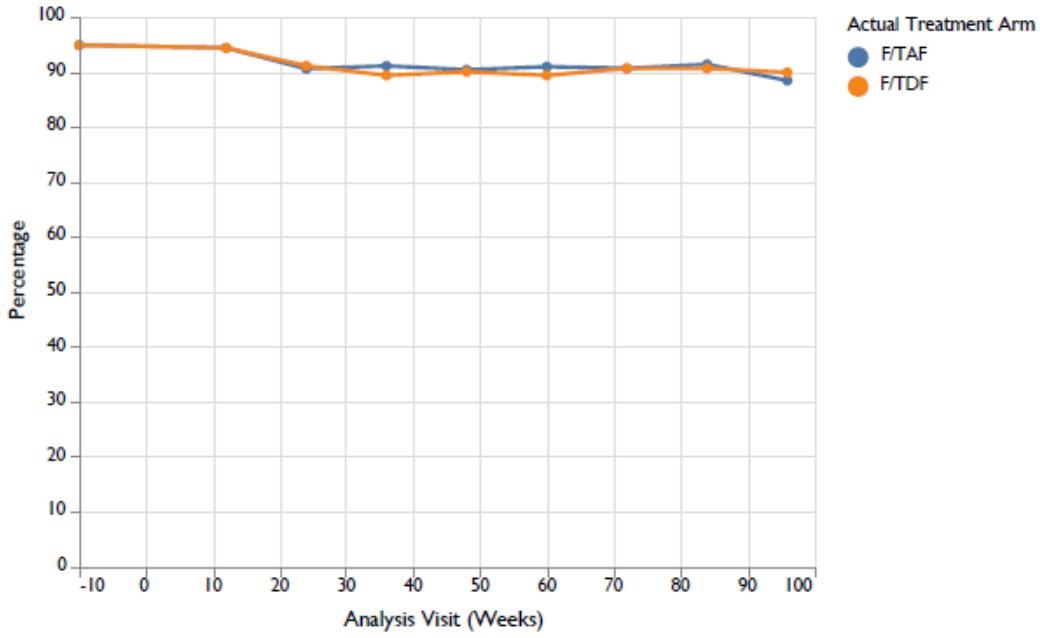
The only secondary endpoint related to efficacy in Study 2055 pertains to the incidence of HIV-1 infection when all subjects have 96 weeks of follow-up in the blinded phase, which has not yet occurred. All other secondary endpoints described in the protocol are related to safety evaluations and are addressed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

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

Sexual Risk Behaviors During Study

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

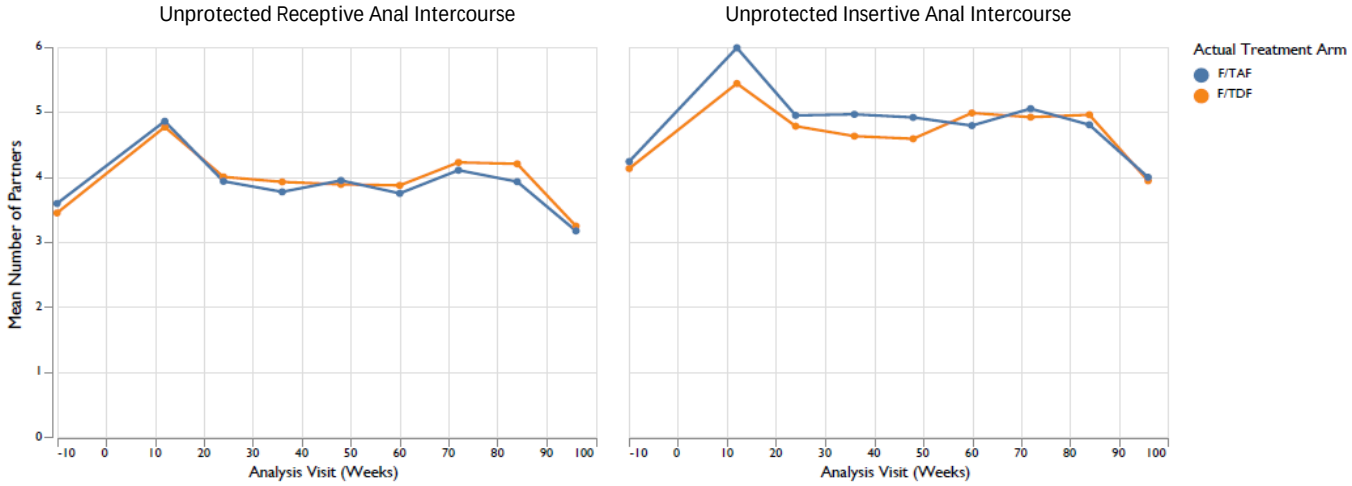
Figure 3: Percentage of Subjects Reporting Condomless Sex Since Last Visit (GS-US-412-2055)



Source: FDA analysis of ADQS dataset – Safety Analysis Set

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

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



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

Sexually Transmitted Infections (STIs) During Study

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

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

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

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

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

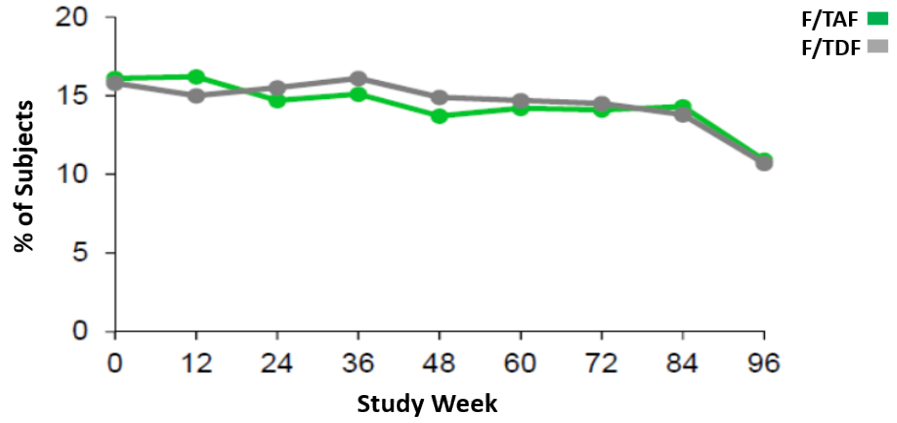
Source: FDA analysis of ADLB dataset

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

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

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

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



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

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

Reviewer comment: *Taken together, the post-baseline sexual risk behaviors and STI rates observed in Study 2055 suggest that the population remained at consistently high risk of HIV-1 acquisition throughout the trial. Furthermore, given that these on-treatment observations were not dissimilar to the baseline findings, there was no evidence of risk compensation occurring during the trial.*

Lastly, the randomized population reported a mean of 4 unique UIAI partners in the 3 months prior to screening. In addition, 92% reported UIAI events during the trial (data not shown) and 16% were diagnosed with chlamydial or gonococcal urethritis. Given these findings, it is reasonable to assume that penile HIV-1 exposures were likely occurring during the trial. While a subgroup analysis by sexual practices was not possible given the trial's eligibility criteria and the large degree of overlap between UIAI and URAI behaviors in most subjects, the low number of observed HIV-1 infections suggests a protective effect of F/TAF and F/TDF for this low-risk exposure category as well.

Dose/Dose Response

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

Durability of Response

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

Persistence of Effect

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

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

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

Additional Analyses Conducted on the Individual Trial

None to report.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

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

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

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

(b) (4)

The major concern regarding the benefit of F/TAF in the postmarket setting is the lack of clinical data in cisgender women, or individuals at risk of HIV-1 acquisition from receptive vaginal intercourse. This is particularly concerning given that adult and adolescent women made up 19% of new HIV diagnoses in the U.S. in 2017 {CDC 2018a}. A postmarketing commitment will be issued for the Applicant to collect effectiveness data in this population. Until such data are submitted, however, the PrEP indication for F/TAF will exclude individuals at risk from receptive vaginal sex. (b) (4)

(b) (4)

(b) (4)

7.2.2. Other Relevant Benefits

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

7.3. Integrated Assessment of Effectiveness

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

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

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

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

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

8. Review of Safety

8.1. Safety Review Approach

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

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

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

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

8.2. Review of the Safety Database

8.2.1. Overall Exposure

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

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

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

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

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

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

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

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

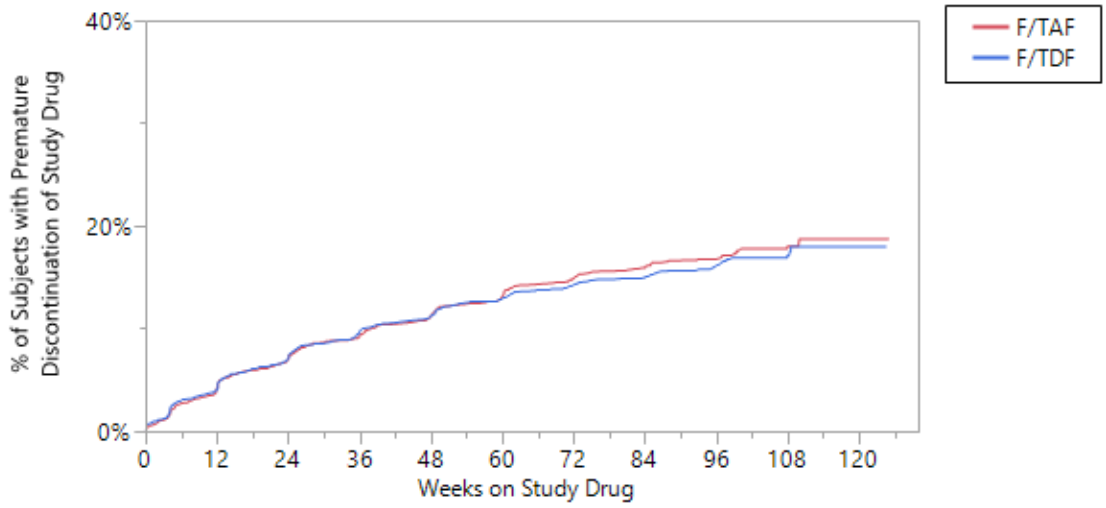
Source: Adapted from Interim Clinical Study Report for GS-US-412-2055 (Table 24, page 124)

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

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

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

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



Source: Reviewer's analysis of ADLS dataset

8.2.2. Relevant characteristics of the safety population:

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

8.2.3. Adequacy of the safety database:

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

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

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

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

8.3.2. Categorization of Adverse Events

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

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

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

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

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

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

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

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

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

8.3.3. Routine Clinical Tests

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

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

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

8.4. Safety Results

8.4.1. Deaths

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

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

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

8.4.2. Serious Adverse Events

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

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

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

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

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

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

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

Source: Reviewer's analysis of ADAE dataset

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

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

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

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

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

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

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

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

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

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

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

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

Section 8.5.1.)

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

8.4.4. Significant Adverse Events

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

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

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

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

Source: Reviewer's analysis of ADAE dataset

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

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

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

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

Source: Reviewer's analysis of ADAE dataset

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

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

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent Adverse Events

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

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

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

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

Source: Reviewer's analysis of ADAE dataset

Adverse Reactions

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

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

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

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

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

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

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

8.4.6. Laboratory Findings

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

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

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

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

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

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

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

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

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

Source: Reviewer's analysis of ADLB dataset

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

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

Source: Reviewer's analysis of ADLB dataset

8.4.7. Vital Signs

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

Body Weight

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

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

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

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

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

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

Source: Reviewer's analysis of ADAE dataset

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

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

8.4.8. Electrocardiograms (ECGs)

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

8.4.9. QT

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

8.4.10. Immunogenicity

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

8.5. Analysis of Submission-Specific Safety Issues

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

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

8.5.1. Renal Safety

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

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

Treatment-Emergent Renal Adverse Events

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

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

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

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

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

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

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

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

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

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

Source: Reviewer's analysis of ADAE dataset

Potential cases of proximal renal tubulopathy (PRT) were reviewed. The Applicant identified subjects with PRT utilizing investigator-reported events for the following MedDRA PTs: Fanconi syndrome, Fanconi syndrome acquired, renal tubular disorder, renal tubular dysfunction, and renal tubular injury. By this method, one subject (Subject (b) (6)) in the F/TDF group was identified with Fanconi syndrome acquired; his narrative is as follows:

- Subject (b) (6) (F/TDF): This 49-year-old man (U.S.) was reported to have Grade 3 nonserious Fanconi syndrome acquired on Study Day 421 (Week 60). The event was marked by graded laboratory abnormalities of low serum phosphate, high serum creatinine, low $eGFR_{CG}$, high urine glucose, high urine protein, and elevated urine β2M to creatinine ration, urine RBP to creatinine ratio, and UPCR. No relevant medical history was reported, and there were no other relevant TEAEs around the time of the event. His estimated adherence rate to study drug was 73%; he had not been on Truvada for PrEP prior to study. The event was considered related to study drug by the investigator and drug was discontinued. The event was considered resolved on Study Day 435, when serum creatinine and $eGFR_{CG}$ improved; however, renal indices had not fully recovered to baseline values as of Study Day 589.

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

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

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

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

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

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

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

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

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

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

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

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

Renal Laboratory Findings

Serum Creatinine and Creatinine Clearance

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

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

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

Source: Reviewer's analysis of ADLB dataset

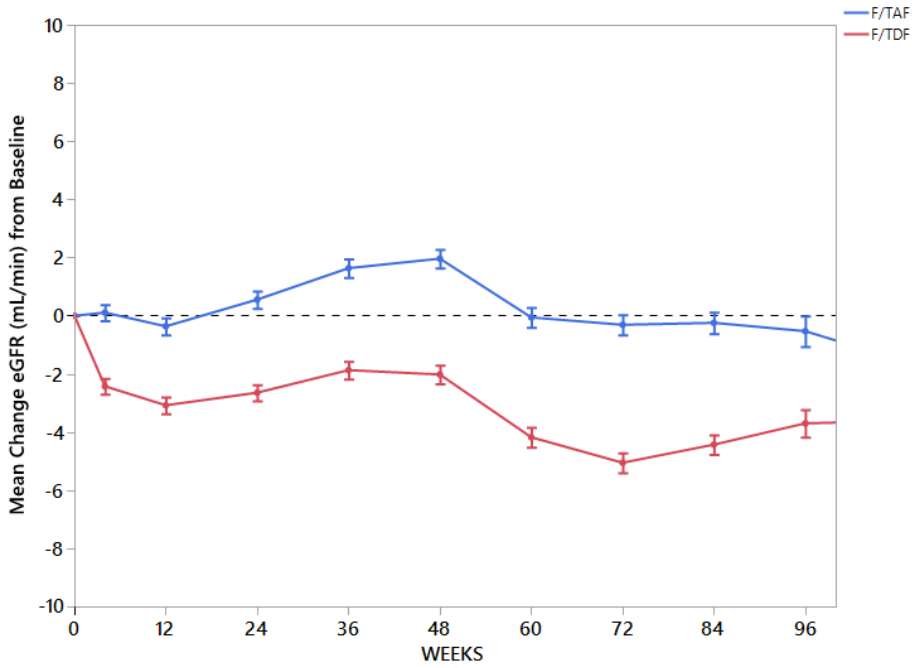
Table 28 displays the corresponding changes in creatinine clearance at each study week. There was minimal change from baseline in $eGFR_{CG}$ through Week 96 in the F/TAF group, whereas there was a mean 2-5 mL/min decrease in the F/TDF group (Figure 7).

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

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

Source: Reviewer's analysis of ADLB dataset

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



Source: Reviewer's analysis of ADLB dataset

Urinary Biomarkers of Proximal Renal Tubulopathy

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

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

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

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

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

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

Source: Reviewer's analysis of ADLB dataset

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

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

Source: Reviewer's analysis of ADLB dataset

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

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

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

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

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

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

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

Graded Renal Laboratory Abnormalities

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

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

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

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

Source: Reviewer's analysis of ADLB dataset

Summary of Renal Safety

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

8.5.2. Bone Safety

Bone Treatment-Emergent Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

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

Source: Reviewer's analysis of ADAE dataset

Bone Mineral Density Substudy

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

Changes in BMD from Baseline

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

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

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

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

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

Categorical BMD Analyses

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

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

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

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

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

Source: Reviewer's analysis of ADDXA dataset

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

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

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

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

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

Summary of Bone Safety

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

8.5.3. Gastrointestinal Events

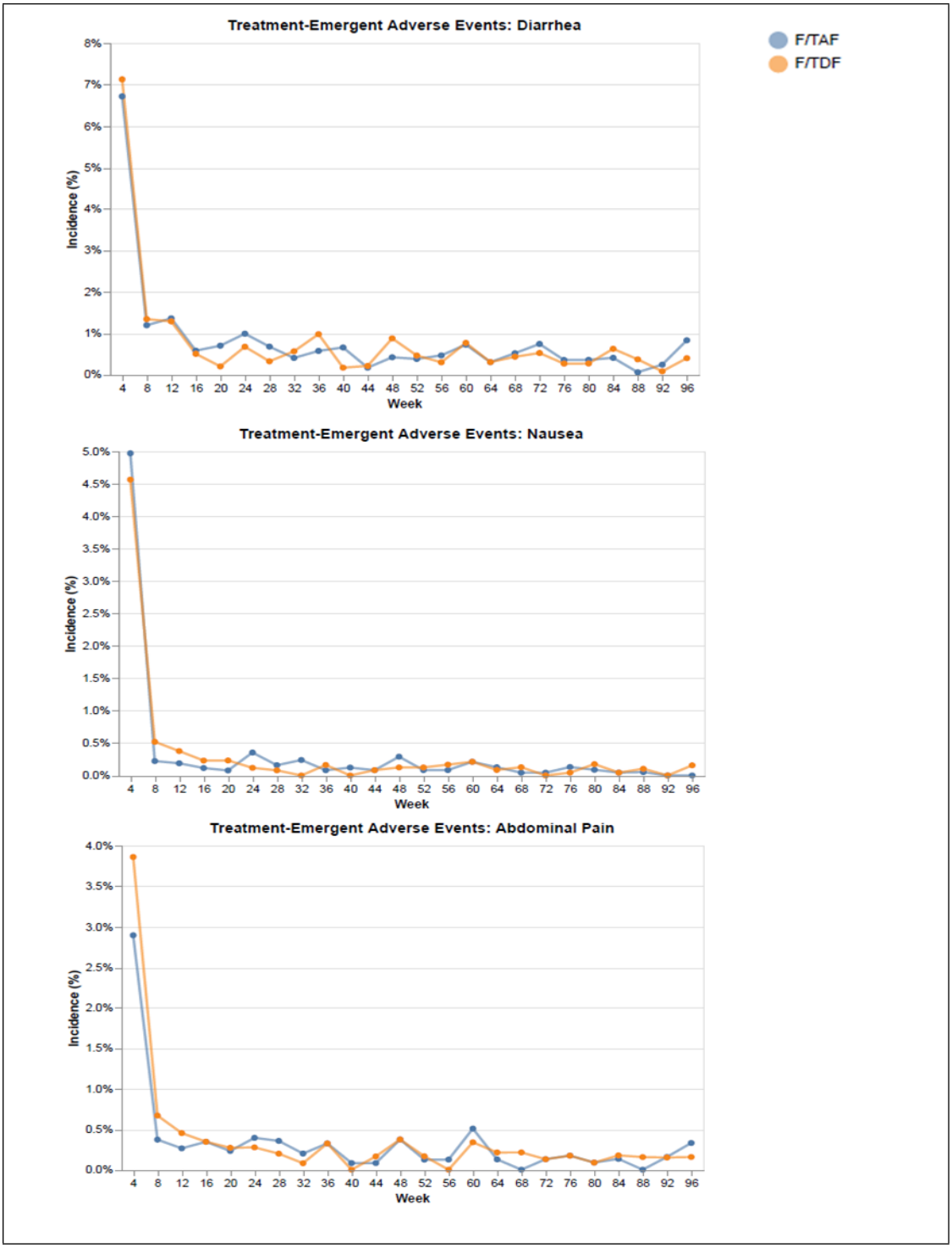
As noted in Section 8.4.5, gastrointestinal AEs were among the most common adverse reactions reported in Study 2055. Previous PrEP trials in an MSM/TGW population reported GI events occurring upon initiation of oral PrEP as part of a self-limited "start-up syndrome" {Grant et al. 2010}. As such, the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

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

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

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

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



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

8.5.4. Fasting Serum Lipids

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

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

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

Source: Reviewer's analysis of ADLB dataset

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

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

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

Source: Reviewer's analysis of ADLB dataset

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

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

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

LDL classifications adapted from the National Cholesterol Education Program.

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

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

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

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

8.6. Safety Analyses by Demographic Subgroups

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

Race

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

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

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

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

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

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

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

Age

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

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

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

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

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

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

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

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

With respect to bone health, consistent with the overall results of the BMD substudy, between-group differences in the mean percentage change from baseline in hip and spine BMD at Week 48 were observed in subjects at both ends of the age spectrum (Table 40). That said, subjects ≥ 50 years of age in the F/TAF group experienced a decline in hip BMD at Week 48 whereas younger subjects in the same treatment group experienced an increase, although the mean percentage changes in either direction were small. In the F/TDF group, subjects < 25 years and those ≥ 50 years of age experienced greater declines in hip and spine BMD compared to the main substudy population.

Table 40: Mean Percentage Change from Baseline in Hip and Spine BMD At Week 48 by Age Group (GS-US-412-2055)

	Hip BMD							
Age Group	<25 years		**≥25** years		>50 years		**≤50** years	
	F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF
Baseline – Mean (SD)	N=21	N=18	N=169	N=167	N=32	N=31	N=158	N=154
	1.07 (0.23)	1.05 (0.14)	1.02 (0.14)	1.02 (0.13)	1.0 (0.13)	0.99 (0.10)	1.04 (0.16)	1.04 (0.14)
Mean (SD) % Change at Week 48	N=17	N=13	N=141	N=145	N=29	N=28	N=129	N=130
	+0.29% (1.97)	-2.24% (3.0)	+0.17% (2.44)	-0.88% (2.36)	-0.28% (1.52)	-1.52% (2.57)	+0.29% (2.53)	-0.87% (2.40)
	Spine BMD							
Age Group	<25 years		**≥25** years		>50 years		**≤50** years	
	F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF
Baseline – Mean (SD)	N=21	N=18	N=169	N=170	N=33	N=32	N=157	N=156
	1.13 (0.21)	1.12 (0.13)	1.13 (0.16)	1.13 (0.14)	1.16 (0.15)	1.12 (0.12)	1.13 (0.16)	1.13 (0.14)
Mean (SD) % Change at Week 48	N=17	N=13	N=142	N=147	N=30	N=29	N=129	N=131
	+0.36% (2.84)	-2.4% (2.71)	+0.51% (3.01)	-1.01% (2.95)	+0.56% (2.60)	-1.87% (3.55)	+0.48% (3.09)	-0.95% (2.78)

Source: Reviewer's analysis of ADDXA dataset

8.7. Specific Safety Studies/Clinical Trials

No specific safety study was conducted.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

As per approved Descovy labeling, long-term carcinogenicity studies of FTC and TDF in mice and rats have not demonstrated any drug-related increases in tumor incidence at FTC and tenofovir exposures within the range of human systemic exposures at the recommended Descovy dose. (Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure is observed in rats and mice after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF.) Neither FTC nor TAF had positive findings on genotoxity studies.

In Study 2055, TEAEs in the MedDRA SOC "Neoplasms benign, malignant and unspecified (including cysts and polyps)" were reported in 160 (6%) and 136 (5%) subjects in the F/TAF and F/TDF groups, respectively. None of the 340 events was considered related to study drug by the investigators; the vast majority (96%) of events were nonserious and 82% consisted of benign skin or soft-tissue neoplasms (including penile warts). Of the remaining events, there was no clustering of any particular neoplasm or differences in frequency between the two arms.

8.8.2. Human Reproduction and Pregnancy

No new information was submitted.

Study 2055 was conducted in biological males only, thus questions about the effect of F/TAF for PrEP on human reproduction and pregnancy were not addressed in this application. The safety of F/TAF in pregnancy can be assumed to be similar between HIV-infected and non-infected individuals. Available clinical data in HIV-infected women from the Antiretroviral Pregnancy Registry (APR) show no increase in the risk of overall major birth defects for FTC compared with the background rate in a U.S. reference population; however, there are insufficient data in the APR to adequately assess the risk of major birth defects with use of TAF. Equally concerning, and relevant to a pregnant population, the efficacy of F/TAF to reduce the risk of sexually-acquired HIV-1 in cisgender women has not been established (see Section 4.5). The indication for F/TAF for PrEP, therefore, will exclude individuals at risk of HIV-1 from receptive vaginal sex. Likewise, labeling will not include language regarding the use of F/TAF for PrEP in pregnant or breastfeeding women.

While some pregnant or breastfeeding women might be at risk of HIV infection from rectal exposure, considerations regarding the use of F/TAF for PrEP in this setting would only apply to women who practice anal sex exclusively. In the absence of data regarding the prevalence of such selective practices, the likelihood seems very low and does not warrant inclusion of specific language in sections 8.1 Pregnancy or 8.2 Lactation of product labeling. Such cases are probably best handled by healthcare providers on an individual case-by-case basis, taking into account the benefit-risk balance of F/TAF in this particular scenario. In contrast, including language in labeling about the use of F/TAF for PrEP in pregnant or breastfeeding women, without providing proper context, may be confusing as it might seem to contradict the approved indication and imply an unsupported claim of efficacy against vaginal sex exposures.

8.8.3. Pediatrics and Assessment of Effects on Growth

No new information was submitted.

Consistent with the agreed-upon Initial Pediatric Study Plan (iPSP), dated December 20, 2016, the Applicant proposes to register F/TAF for PrEP for use in at-risk adolescents weighing at least 35 kg. Clinical trials to evaluate the safety and efficacy of F/TAF for a PrEP indication have not been conducted in adolescents. Instead, the Applicant proposes to extrapolate adult PrEP efficacy data from Study 2055 in MSM/TGW and available safety and PK data with F/TAF in HIV-infected pediatric subjects to support an adolescent indication.

While no PK studies were conducted in adolescents for this indication, the dose of F/TAF is the same for adolescents and adults, and available data suggest that there are no clinically relevant differences in the plasma PK of FTC or TAF, or in PBMC-associated TFV-DP exposures, between HIV-infected adolescents weighing at least 35 kg and HIV-infected adults. Likewise, there are no clinically relevant PK differences between HIV-infected and non-infected adults. Therefore, it is reasonable to expect that PK parameters will be similar between non-infected adolescents and non-infected adults, thus allowing for the extrapolation of adult PrEP efficacy data. This extrapolation approach is also scientifically valid because sexual acquisition of HIV-1 is similar between adults and adolescents. Safety in adolescents is supported by findings from Study 2055 and other clinical trials of F/TAF in HIV-infected pediatric subjects. Taken together, based on PK and clinical considerations, it is reasonable to expand the PrEP indication to include adolescents weighing at least 35 kg. As discussed in Section 4.5, however, efficacy in MSM/TGW cannot be extrapolated to cisgender women based on the available PK data; therefore, the adult efficacy data from Study 2055 cannot be extrapolated to support an indication in female adolescents. This limitation to the adolescent indication will be noted in Descovy labeling.

A partial waiver request for studies in infants and children up to 12 years of age was submitted with this application. As PrEP is intended to reduce the risk of sexually-acquired HIV-1 infection, clinical efficacy trials would be highly impracticable in a younger pediatric population who are not sexually mature and active, or in whom the likelihood of at-risk sexual behavior is very low.

A meeting of the FDA Pediatric Research Committee (PeRC) was held on September 4, 2019, to discuss this application. The PeRC agreed to grant the requested waiver in children from birth to < 12 years of age and concurred with the extrapolation approach to support the use of F/TAF for PrEP in at-risk adolescents, excluding those at risk from receptive vaginal sex, weighing at least 35 kg.

Lastly, while F/TAF safety and efficacy data can be reasonably extrapolated from other sources, adherence to a daily oral PrEP regimen is likely to differ between at-risk adolescents and their adult counterparts in Study 2055. In two previously conducted open-label trials of F/TDF for

PrEP in adolescents, the ATN 113 trial in MSM aged 15-17 years in the U.S. {Hosek et al. 2017} and the Choices for Adolescent Prevention Methods for South Africa (CHAMPS) PlusPills trial in South African boys and girls aged 15-19 years (NCT02213328) {Gill et al. 2017}, a trend toward lower adherence to a daily oral PrEP regimen was observed as study visits became less frequent, suggesting that monthly visits may be needed to support greater adherence among adolescents. These insights into adolescent adherence, as gleaned from the ATN 113 trial, informed Truvada labeling in 2018 {Gilead Sciences, Inc. 2018}, and can be transferred to Descovy labeling as both drugs share the same once daily dosage schedule.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No new safety issues have been identified from the available data regarding overdose. No new information regarding drug abuse potential, withdrawal, or rebound was submitted, but drug abuse is not expected with F/TAF for PrEP.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Descovy was approved for the treatment of HIV-1 infection in 2016. Since first marketing approval, the cumulative exposure to drug product is estimated to be 309,417 patient-years of treatment. In addition, TAF has been marketed in various fixed-dose combination products for an HIV-1 treatment indication since at least 2015, and as monotherapy for the treatment of chronic hepatitis B infection since 2016. In general, TAF and F/TAF have been well-tolerated in the postmarket period, and no major new safety issues have emerged based on periodic safety update reports (PSURs) and periodic benefit-risk evaluation reports (PBRERs) submitted to this and other NDAs for TAF-containing products. The overall benefit-risk assessment for F/TAF remains positive.

That said, per the most recent Periodic Adverse Drug Experience Report (PADER) submitted to this NDA (dated January 21, 2019), rash, urticaria, and angioedema have been identified as adverse reactions to TAF in postmarketing. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have already been added to Section 6.2 (Postmarketing Experience) of labeling for other TAF-containing products (e.g., Vemlidy, Genvoya, Biktarvy) and will be added to Descovy labeling as part of this application.

In Study 2055, 6% of subjects in each treatment arm experienced an allergic-type TEAE under the MedDRA SOC “Skin and subcutaneous tissue disorders”, including rash, urticaria, and angioedema. The vast majority (91%) of these events were not considered related to study drugs by the investigators. The frequencies of these events by MedDRA HLT were comparable between the treatment groups, and no between-group differences were noted when SMQs

(broad and narrow) of severe cutaneous adverse reaction, anaphylactic reaction, or angioedema were analyzed. About 20% of these events occurred within the first 30 days of study drug administration, with comparable distributions in both arms; however, of these early onset events, 36% (15/40) in the F/TAF group versus 19% (7/36) in the F/TDF group were considered related to study drug by the investigators. Five subjects had nonserious skin events that led to study drug discontinuation within the first 30 days of administration: 4 subjects with rash (2 per treatment group), and 1 subject with generalized pruritus in the F/TDF group; all but one case of rash in the F/TDF group were considered related to study drug.

One subject in the F/TDF arm (Subject (b) (6)) also experienced a serious Grade 2 event of Stevens-Johnson syndrome on Day 5. The event was not considered related to study drug and did not result in study drug discontinuation (only interruption). The subject had initiated treatment for syphilis with doxycycline on Day 1, which might provide an alternative etiology.

8.9.2. Expectations on Safety in the Postmarket Setting

As HIV-1 infection status has no clinically relevant impact on the PK of FTC and TAF and given the favorable safety profile of other F/TAF-containing products on the market when used for HIV-1 treatment, the safety profile of F/TAF for HIV-1 PrEP is also expected to be favorable in the postmarket setting. Safety issues related to renal and bone toxicity, and increases in fasting lipid parameters and body weight, should continue to be monitored.

8.9.3. Additional Safety Issues From Other Disciplines

None identified.

8.10. Integrated Assessment of Safety

In Study 2055, once-daily F/TAF for PrEP was well tolerated in 2,694 healthy participants, with a median exposure of 86 weeks, as demonstrated by the low proportions of subjects with study drug-related SAEs (0.1%) or TEAEs leading to study drug discontinuation (1.3%). The most common, non-infectious TEAEs, with an incidence of ≥ 5%, in subjects randomized to F/TAF were diarrhea (16%), nausea (7%), headache (7%), and fatigue (5%); the most common drug-related TEAEs, or ARs, with an incidence ≥ 2%, were diarrhea (5%), nausea (4%), fatigue, headache, and abdominal pain (2% each). Most TEAEs reported in this trial were mild (Grade 1). For all of the above safety findings, and indeed for nearly all reported adverse events, there were no notable differences between the F/TAF and F/TDF groups. The safety findings reported in this trial, in particular those related to subclinical changes in renal biomarkers and bone density, are consistent with previous trials that have compared TAF to TDF. Moreover, the safety profile of F/TAF in HIV-uninfected participants was similar to that reported for PLWH; i.e., no new safety concerns were identified.

The important safety issues identified in this review are as follows:

Nephrotoxicity: Higher plasma concentrations of TFV, as seen with TDF administration, have been associated with nephrotoxicity. Conversely, lower circulating TFV levels, as seen with TAF, are hypothesized to result in fewer renal adverse events. In Study 2055, small but significant differences were observed at each visit between the treatment groups with respect to changes from baseline in serum creatinine and $eGFR_{CG}$, favoring F/TAF. In addition, F/TAF was noted to have favorable effects on changes from baseline at Week 48 in numerous renal biomarkers of proximal tubular function (UPCR, β2M and RBP to creatinine ratios) relative to F/TDF, although the clinical significance of these changes is uncertain. While there were no reports of PRT in the F/TAF group (compared to one case of Fanconi syndrome in the F/TDF group), the overall rates of renal-associated TEAEs, SAEs, or events leading to drug discontinuation, as well as of graded renal laboratory abnormalities, were low but generally comparable between the treatment groups. It is possible that with longer duration of use these differences in renal biomarkers may translate into improved renal clinical outcomes, but this remains mostly speculative at the moment. That said, given the substantial rates of PrEP non-persistence being reported beyond one year, it is unclear how relevant these subclinical changes will be to an HIV-uninfected population that may only be using F/TAF for PrEP for a limited duration {Coy et al. 2019}. In sum, the renal safety profile of F/TAF is certainly no worse than that of F/TDF, but whether its favorable biomarker profile translates into clinical benefit remains to be determined. For now, product labeling for F/TAF will retain the warning and precaution related to renal impairment (5.3). Routine laboratory monitoring as recommended in labeling should suffice to manage this potential safety risk.

Bone Mineral Density Changes: Available preclinical and clinical data suggest that TDF use is associated with reductions in BMD. The clinical significance of this for most individuals remains unclear as reports have been mixed about a possible association between TDF use and fragility fractures {Grant et al. 2016}. Consistent with previous trials, Study 2055 demonstrated small, but statistically significant differences between F/TAF and F/TDF with respect to BMD changes from baseline at 48 weeks, favoring F/TAF. The improvements in BMD seen with F/TAF were observed across all age subgroups. Clinically, there were no differences between the treatment groups with respect to fracture rates or the reporting of other events related to bone health. Given the uncertain relationship between BMD reductions and fracture risk, labeling for F/TAF and other TAF-containing products no longer includes a warning related to bone loss, but BMD changes are still reported in Section 6 Adverse Reactions. Product labeling is considered adequate to convey this potential safety risk.

Fasting Serum Lipid Changes: Consistent with previous clinical trials, Study 2055 demonstrated differences between F/TAF and F/TDF in serum fasting lipid changes from baseline, favoring F/TDF. Higher proportions of subjects in the F/TAF group also had graded increases in fasting total cholesterol or LDL cholesterol during the course of the trial compared with the F/TDF

group. The reasons for these differences have not been fully elucidated but circulating TFV has been hypothesized to have lipid-lowering properties. As TAF administration results in lower TFV plasma concentrations, per this hypothesis F/TAF would have less of an impact on countering increasing lipid levels over time than F/TDF. The clinical significance of these differences is not entirely clear as there were no between-group differences in fasting total cholesterol to HDL ratio, which is associated with cardiovascular risk, or in cardiovascular or cerebrovascular events, which were rare. Moreover, the percentage of subjects initiating lipid-lowering agents during the trial was low in both arms (1-2%). Labeling for F/TAF will describe the fasting lipid changes observed in Study 2055 in Section 6 Adverse Reactions, consistent with labeling of other TAF-containing products. Product labeling is considered adequate to manage this potential safety risk.

Body Weight Increase: Although subjects in the F/TAF group of Study 2055 experienced a mean increase of 1.1 kg in body weight at 48 weeks, in contrast to no change in the F/TDF group, this increase appears to be consistent with expected weight gains in a healthy population between 20 and 40 years of age. Rather than F/TAF directly causing increased weight, the differences in weight changes between the treatment groups of Study 2055 may be due to a suppressive effect of F/TDF on expected weight gain in this population. As such, based on the data from Study 2055, there does not appear to be an F/TAF-related risk of weight increase in the HIV-uninfected male population evaluated in this trial.

Conclusion

The F/TAF safety data reviewed as part of this application are consistent with previous clinical trials that showed improved measures of renal tubular function (as demonstrated by changes in urinary biomarkers over time) and minimal impact on BMD (as observed on DXA imaging) with TAF dosing relative to TDF. While these subclinical differences were statistically significant, and favored F/TAF, the clinical benefit of F/TAF over F/TDF was not apparent in the context of a 96-week trial, where no clinically-relevant differences were noted between F/TAF and F/TDF in the frequency or types of adverse events related to renal or bone safety, or in the frequency or severity of abnormalities for most laboratory tests commonly used in clinical practice. Indeed, the clinical safety profile of F/TAF and F/TDF were remarkably similar in Study 2055 with respect to common adverse events, SAEs or adverse events leading to drug discontinuation (the latter two of which occurred at very low rates). These findings are consistent with a recent meta-analysis of 11 trials that compared TAF to TDF {Hill et al. 2018}. Also consistent with previous trials, there was a higher incidence of elevated fasting lipids in Study 2055 among subjects taking F/TAF compared with those taking F/TDF; however, these findings were not associated with greater cardiovascular risk in this relatively short-term trial. Finally, the potential safety risks identified for F/TAF in this review are not new and most are not serious; they can be adequately managed through product labeling and routine pharmacovigilance.

9. Advisory Committee Meeting and Other External Consultations

A meeting of the Antimicrobial Drug Advisory Committee (AMDAC) was held on August 7, 2019, to discuss this supplemental application. The main objective was to discuss whether the available data supported approval of F/TAF for HIV-1 PrEP in at-risk adults and adolescents. In particular, the FDA was interested in the committee's input regarding the adequacy of the data to support a PrEP indication in subpopulations defined by route of HIV transmission risk (i.e., receptive anal intercourse, insertive penile intercourse, and receptive vaginal intercourse). With respect to the latter, as clinical data with F/TAF for PrEP in cisgender women are lacking, the FDA sought advice on the acceptability of the PK extrapolation strategy proposed by the Applicant to support the broad indication being sought.

The AMDAC voted 16-2 in support of approval of F/TAF for PrEP in MSM/TGW. The two committee members who opposed approval cited insufficient data in TGW and African-Americans, who are disproportionally affected by HIV in the United States. The ADMAC noted the importance of F/TAF being noninferior, but not superior, to F/TDF in Study 2055, and advised that product labeling should explicitly convey that finding. Some committee members expressed concern about the elevated serum lipids and weight gain observed with F/TAF and considered that these should be followed closely in the postmarket setting, along with collection of longer-term data concerning kidney and bone safety.

The AMDAC, however, voted 10-8 against approval in cisgender women (or those at risk of HIV-1 from receptive vaginal sex). The PK data failed to sway the majority of committee members, who were not entirely convinced by the Applicant's assertion that systemic drug exposure alone drives PrEP efficacy. Most of those who voted in favor of an approval in cisgender women did so mostly out of concern that a limited approval would set up a two-tier system and exacerbate gender inequities in health care. Regardless of how they voted, the committee was unanimous in voicing a need for high-quality clinical trial data in cisgender women, and some members expressed disappointment that an application for an HIV-1 PrEP agent would be submitted without such data. The Applicant stated at the meeting that it was committed to study F/TAF for PrEP in a female population.

Lastly, the AMDAC concurred that data from Study 2055 could be applied to men at risk of HIV-1 from insertive (vaginal or rectal) sex.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

U.S. Prescribing Information

The draft U.S. Prescribing Information (USPI) for Descovy, received April 5, 2019, was reviewed and revised as follows (refer to final labeling for details):

Labeling Section	FDA Comment
All Sections	In general, the information contained in the USPI was accurate; however, where the presentation of information was considered misleading or promotional, FDA proposed alternate language. Much of the language related to the PrEP indication mirrors that of the approved Truvada USPI.
INDICATIONS AND USAGE	The Applicant's proposed indicated population for PrEP (i.e., at-risk adults and adolescents weighing at least 35 kg) was inappropriately broader than the studied population. Specifically, the efficacy of F/TAF for PrEP in cisgender women could not supported by the totality of the evidence (see Section 4.5). As such, FDA limited the PrEP indication for Descovy by excluding individual at risk of HIV-1 acquisition from receptive vaginal sex. A Limitation of Use statement was considered reasonable to alert prescribers that effectiveness in this population has not been evaluated. Moreover, in contrast to the Truvada indication, the PrEP indication for Descovy does not include "in combination with safer sex practices" as this is not reflective of how the product was used in the pivotal trial or how PrEP is generally used in practice. Further information about the proper use of Descovy for PrEP is included in the Warnings and Precautions subsection 5.2
DOSAGE AND ADMINISTRATION	The Applicant's revisions to this section were appropriate and aligned with recommendations found in the Truvada USPI
BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS	A new Boxed Warning and Contraindication were proposed to align with the approved Truvada PI. A new Warning and Precaution 5.2 – Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When Descovy is Used for HIV-1 PrEP – was included. Much of the information is consistent with the corresponding warning in the Truvada USPI but streamlined in some areas (e.g., discussion of HIV-1 risk factors) given the greater familiarity with PrEP since the time of the Truvada approval. Given that wording regarding safer sex practices is not part of the PrEP indication for Descovy, FDA considered it prudent to include a statement that the time from initiation of Descovy to maximal protection against HIV-1 infection is unknown.
ADVERSE REACTIONS	The proposed Clinical Trials Experience subsection describes the rates of common ARs in Study 2055; FDA added abdominal pain, which was omitted

	from the Applicant's proposal due to splitting of preferred terms. Changes from baseline at Week 48 in serum creatinine, $eGFR_{CG}$, UPCR and BMD are also described. The FDA did not agree with the inclusion of information related to (b) (4) or the use of ≥ (b) (4) change from baseline to describe the BMD changes, preferring to use ≥ 7% and ≥ 5% cutoffs for the hip and spine regions, respectively (see Table 35), which the FDA considers to be more clinically meaningful. In addition, FDA recommended including the changes from baseline in fasting serum lipids. Lastly, the Postmarketing Experience subsection (6.2) was updated to include the terms angioedema, urticaria, and rash (see Section 8.9.1).
USE IN SPECIFIC POPULATIONS	The FDA did not agree with the Applicant's proposals to update Sections 8.1 Pregnancy and 8.2 Lactation (b) (4) (b) (4). The language proposed for Section 8.4 Pediatric Use was appropriate.
CLINICAL PHARMACOLOGY	The Applicant's proposal to update Section 12.4 Microbiology with data from the CDC rectal challenge macaque study with F/TAF was appropriate; however, the FDA did not agree with inclusion of data (b) (4) (b) (4) given the limited PrEP indication being approved.
CLINICAL STUDIES	The important design features and baseline disease characteristics of Study 2055 were included, as well as description of the high STI rates observed during the trial. The section provides a fair representation of the overall efficacy results (i.e. noninferiority of Descovy to Truvada in reducing the risk of HIV-1) and subgroup analyses. FDA simplified the proposed language regarding drug adherence (from the DBS case-control substudy) to note that subjects who became HIV-infected had substantially lower median intracellular levels of TFV-DP compared with matched HIV-uninfected controls, (b) (4) (b) (4).

Medication Guide

The Patient Package Insert (PPI) for Descovy was converted to a Medication Guide (MG) with this application. The proposed revisions were largely consistent with the Descovy USPI and the Truvada MG; however, FDA revised language to emphasize the limitations of use, namely that Descovy for PrEP is not indicated for use in biological females at risk of HIV-1 acquisition from receptive vaginal sex. Refer to the FDA Patient Labeling Review for details.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

The main risk associated with any antiretroviral drug used for PrEP is that the product will be initiated or continued in the face of undiagnosed HIV-1 infection, thus increasing the risk of developing drug resistance. This was the concern that led to the creation of a Risk Evaluation and Mitigation Strategy (REMS) when F/TDF was approved for PrEP in 2012. That REMS initially consisted of a Medication Guide, communication plan, a timetable for assessments of the REMS, and elements to ensure safe use (ETASU), the latter of which consisted of educational and training materials made available for voluntary use by prescribers and users of PrEP.

At the time of the initial PrEP approval, public information and awareness of PrEP were very limited and a REMS was considered necessary to ensure that the benefits outweighed the risks. In the last five years, however, awareness and uptake of PrEP have increased substantially. The reasons for this are manifold but undoubtedly include the proliferation of external resources, from the CDC to state and city health departments to advocacy groups, that have provided educational materials about PrEP, issued PrEP clinical guidelines, and promoted PrEP use among high-risk individuals. Importantly, knowledge about the risks and appropriate use of PrEP among prescribers and users has increased to satisfactorily levels during this period, as demonstrated by surveys conducted for the periodic REMS assessments. Whether survey respondents obtained their information from the REMS or other external sources is not clear. Regardless, based on the availability of multiple non-REMS educational programs, the publication of PrEP clinical guidelines by the CDC and other health authorities, and the acceptable levels of PrEP knowledge demonstrated by prescribers and users, the FDA determined in 2019 that a REMS was no longer necessary to maintain a favorable benefit-risk balance. The REMS for F/TDF for PrEP was released on July 1, 2019, although the Medication Guide remains part of product labeling [refer to the REMS reviews for NDA 21752/S-060 by the Division of Antiviral Products (DAVP) and Division of Risk Management (DRISK)].

The above considerations also apply to F/TAF for PrEP. As such, a REMS is not deemed necessary to manage the potential risks associated with use of F/TAF for PrEP, which can be adequately managed in the postmarket setting through labeling, including a Medication Guide.

12. Postmarketing Requirements and Commitments

The data submitted in this application have met the statutory requirements to support a PrEP indication for F/TAF in individuals at risk of HIV-1 acquisition from receptive anal intercourse or insertive penile intercourse and are thus sufficient to allow for regulatory action to be taken. However, data that convincingly demonstrate the efficacy of F/TAF for PrEP in individuals at risk of HIV-1 from receptive vaginal intercourse (e.g., cisgender women) are lacking. The PrEP indication for F/TAF will therefore exclude this population and product labeling will note this limitation of use.

The availability of additional HIV prevention options for at-risk women is of paramount importance to global efforts to curb the HIV epidemic. At the AMDAC meeting, committee members were unanimous in their call for clinical trial data in cisgender women to evaluate the safety and effectiveness of F/TAF for PrEP in that population. Depending on how they voted, the ADMAC members considered that these data could be collected pre- or post-approval. Given that this application is ready for approval, albeit with a limited indication, and that an approved safe and effective drug (F/TDF) is currently available for use in at-risk women, rather than delay the approval of this application, the FDA has determined that a clinical trial of F/TAF for PrEP in cisgender women can be conducted as a postmarketing commitment.

The FDA is cognizant of the challenges in designing a feasible PrEP trial in cisgender women. At the time of this writing, discussions were underway with the Applicant to explore novel trial designs that could support an expanded indication in this population. While details are still being negotiated, FDA is requesting a randomized trial in at-risk women and adolescent girls with F/TDF as a control. The trial, however, would be powered to demonstrate efficacy relative to background HIV-1 incidence rates as estimated by at least two distinct methods, such as the background HIV-1 incidence rates from sites involved in recent clinical trials, cross-sectional HIV surveillance surveys, or from high-quality local epidemiology data. Given this is novel approach to estimating PrEP efficacy in a clinical trial setting, two distinct external controls would serve to corroborate the observed treatment effect and increase confidence in the results.

13. Appendices

13.1. GS-US-412-2055 Study Procedures

			Double-Blind Treatment End of Week[a]									Post Week 96	Open-Label Treatment End of Week[c]							
Study Procedure	**Screening**	**Day 1**	**4**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**Every 12 Weeks**	**End of Blinded Treatment Phase Visit[b]**	**12**	**24**	**36**	**48**	**Every 12 Weeks[d]**	**30-Day Follow-up[e]**	**ESDD[f]**
Informed Consent	X																			
Medical History	X																			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X						X				X						X			
Targeted Physical Exam		X[h]	X	X	X	X		X	X	X		X	X	X	X	X		X	X	X
Vital Signs[g]	X	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																			
Genital, Rectal, and Pharyngeal Examination for STIs as appropriate	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharyngeal Swab for Gonorrhea and Chlamydia[gc] (Local Laboratory)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rectal Swab for Gonorrhea and Chlamydia (Local Laboratory)[gc]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample for Gonorrhea and Chlamydia	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rapid HIV-1 Ag/Ab Test (In-Clinic)[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 Ab/Ag[i]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 RNA by PCR[r]	X	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dipstick Urinalysis (In-Clinic)	X																			
Urinalysis, Urine Protein, Urine Chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Storage Sample			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Chemistry Profile[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Hematology Profile[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for DBS[j]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood Sample for Syphilis testing[k] (Local Laboratory)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B Testing (HBsAg/HBsAb/HBcAb)	X				X		X		X		X	X[sd]	X[sd]		X		X	X[sd]		
Hepatitis C Testing (HCV Ab)	X						X				X	X[sc]	X[sc]				X	X[sc]		
Estimated GFR	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Lipids (fasting not required at screening)	X				X		X		X		X	X[t]			X		X	X[t]		
Trough PK blood sample (PBMC and plasma)[j]			X																	
Anytime PK blood sample (plasma only)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Plasma Storage Sample[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

			Double-Blind Treatment End of Week[a]									Post Week 96	Open-Label Treatment End of Week[c]							
Study Procedure	Screening	Day 1	4	12	24	36	48	60	72	84	96	Every 12 Weeks	End of Blinded Treatment Phase Visit[b]	12	24	36	48	Every 12 Weeks[d]	30-Day Follow-up[e]	ESDD[f]
CASI Questionnaire[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Randomization in IXRS		X																		
Risk Reduction/ Adherence Counseling	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
DXA Scan (Hip and Spine)		X[i]					X[a]				X[a]		X[a]				X[a]			X[i]
Study Drug Dispensation and Accountability		X[j]	X	X	X	X	X	X	X	X	X	X	X[k]	X	X	X	X[aa]	X		X[ab]
CD4, CD8, and CD4/CD8 (HIV Infected Only)			Performed at all visits after HIV infection.																X	X
Latent and Active Reservoir assessment (HIV Infected Only)			Performed for HIV infected participants only. Performed at first study visit after HIV infection and at regularly scheduled study visits 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter.																	X
T cell response and phenotype (HIV Infected Only)			Performed for HIV infected participants only. Performed at first study visit after HIV infection and at regularly scheduled study visits 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter.																	X
Viral Sequence Diversity assessment (HIV Infected Only)			Performed for HIV infected participants only. Performed at first study visit after HIV infection and at regularly scheduled study visit 24 weeks after HIV infection only.																	X
Inflammatory/Immune Activation Biomarkers (HIV Infected Only)			Performed for HIV infected participants only. Performed at first study visit after HIV infection and at regularly scheduled study visits 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter.																	X

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

13.2. References

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Guidances for Industry

Guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Systemic Drug Products for Pre-Exposure Prophylaxis* (March 2019)

13.3. Financial Disclosure

In accordance with 21 CFR 54.4, the Applicant has submitted the Financial Certification and Disclosure summary information for all investigators who participated in the covered clinical study for this application, Study GS-US-412-2055.

Covered Clinical Study (Name and/or Number): Study GS-US-412-2055 (DISCOVER)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 673		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 42		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 2 Significant payments of other sorts: 36 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 4		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason: Not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

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

/s/

PETER S MIELE
10/02/2019 10:28:40 AM

WENDY W CARTER
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