STATISTICAL ANALYSIS PLAN

Study 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
Name of Test Drug:	Emtricitabine/Tenofovir Alafenamide (F/TAF)
Study Number:	GS-US-412-2055
Protocol Version (Date):	Amendment 5 (05 September 2018)
Analysis Type:	End of Blinded Treatment Phase Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	11 December 2019
Analysis Plan Author(s):	PPD / PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARV	antiretroviral
AST	aspartate aminotransferase
ATR	ATRIPLA
AUDIT	Alcohol Use Disorders Identification Test
BLQ	below limit of quantitation
BlOCF	baseline observation carried forward
BMD	bone mineral density
BMI	body mass index
CASI	Computer-Assisted Self-Interview
CDC	Center for Disease Control
CG	Cockcroft-Gault
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
DB	double-blinded
DBS	dried blood spot
DNA	deoxyribonucleic acid
DXA	dual energy x-ray absorptiometry
E/C/F/TAF	elvitegravir (EVG) 150 mg/cobicistat (COBI) 150 mg/emtricitabine (FTC) 200 mg/tenofovir alafenamide (TAF) 10 mg single tablet regimen
E/C/F/TDF	elvitegravir (EVG) 150 mg/cobicistat (COBI) 150 mg/emtricitabine (FTC) 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg single tablet regimen
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate using Cockcroft-Gault formula
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC-TP	Emtricitabine triphosphate
F/TAF	fixed dose combination of emtricitabine (FTC; F)/tenofovir alafenamide (TAF)
F/TDF	emtricitabine/tenofovir disoproxil fumarate

FTC, F	emtricitabine
GFR	glomerular filtration rate
Gilead	Gilead Sciences, Inc.
GEN	Genvoya, E/C/F/TAF
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HDL	high density lipoprotein
HIV-1	human immunodeficiency virus (Type 1)
HLGT	high level group term
HLT	high level term
IAI	insertive anal intercourse
ID	identification
IDMC	independent data monitoring committee
IWRS	interactive web response system
LDL	low density lipoprotein
LLT	lowest level term
LOCF	last observation carried forward
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NI	non-inferiority
OL	open-label
OLE	open-label extension
PBMCs	peripheral blood mononuclear cells
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
PK	pharmacokinetic
PP	per protocol
PRT	proximal renal tubulopathy
PT	preferred term
PVE	Pharmacovigilance and Epidemiology. A department at Gilead Sciences that was renamed to Pharmacovigilance and Epidemiology (PVE), effective 01 December 2017.
PY	person-years
Q	quartile
Q1	first quartile
Q3	third quartile

QD	once daily
RAI	receptive anal intercourse
RBP	retinol binding protein
RNA	ribonucleic acid
rSTI	rectal sexually transmitted infection
SAE	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SMQ	Standardised MedDRA Query
SOC	system organ class
STI	sexually transmitted infection
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TFV	tenofovir
TFV-DP	tenofovir diphosphate pharmacologically active metabolite (TFVpp)
TFL	tables, figures, and listings
TFV	tenofovir
TGW	transgender women
UIAI	unprotected insertive anal intercourse
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
URAI	unprotected receptive anal intercourse
US	United States
VEM	Vemlidy, TAF
WHO	World Health Organization

1. INTRODUCTION

The primary analysis of HIV-1 pre-exposure prophylaxis (PrEP) in Study GS-US-412-2055 has been done (clinical study report [CSR] date: 25 March 2019) after all subjects had either a minimum follow-up of 48 weeks and at least 50% of the subjects had 96 weeks of follow-up after randomization or prematurely discontinued from the study. This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the end of blinded phase analysis, which will be performed when all subjects have either completed the end of blinded treatment visit or prematurely discontinued from the study. The end of blinded phase is also the end of randomized phase, and we will use the phrases double-blinded (DB) phase and randomized phase interchangeably. Although the study was unblinded for the primary analysis, blind was maintained at the participant, investigator and operational staff at Gilead.

This SAP is based on the study protocol amendment 5 dated 5 September 2018, the electronic case report form (eCRF), data transfers for laboratory tests, the Computer-Assisted Self-Interview (CASI) questionnaire, and dual energy x-ray absorptiometry (DXA). The SAP will be finalized before database finalization for the final unblinding of the end of blinded phase analysis.

1.1. Study Objectives

The primary objective of this study is:

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

The secondary objectives of this study are:

- To compare bone safety between the treatments as determined by dual energy x-ray absorptiometry (DXA) tests of hip and spine bone mineral density (BMD) in a subset of participants at Week 48 and Week 96 in the blinded phase

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

- To assess the rates of HIV-1 infection in men (MSM) and transgender women (TGW) who have sex with men who are administered daily F/TAF or F/TDF when all subjects have 96 weeks of follow-up after randomization

- To compare the general safety between the treatments

Exploratory objectives of this study include:

[redacted]

1.2. Study Design

Design Configuration and Subject Population

GS-US-412-2055 is a randomized, double-blinded, multicenter study to evaluate the safety and efficacy of F/TAF FDC versus F/TDF FDC for pre-exposure prophylaxis in HIV-1 negative adult men and transgender women who have sex with men and are at risk of HIV-1 infection.

Treatment Groups

Subjects who provide written consent and meet all eligibility criteria are randomized in a 1:1 ratio to one of the following 2 treatment groups:

- **Treatment Group 1:** FDC of emtricitabine 200 mg / tenofovir alafenamide 25 mg (F/TAF) + Placebo-to-match FDC of emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (F/TDF), administered orally once daily (n 2500)
- **Treatment Group 2:** FDC of emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (F/TDF) + Placebo-to-match FDC of emtricitabine 200 mg / tenofovir alafenamide 25 mg (F/TAF), administered orally once daily (n 2500)

Key Eligibility Criteria

Subjects at high risk of sexual acquisition of HIV who meet the following criteria:

- HIV-1 negative status
- MSM or TGW (male at birth) who have at least one of the following:
  a) condomless anal intercourse with at least two unique male partners in the past 12 weeks (partners must be either HIV-infected or of unknown HIV status)
  b) documented history of syphilis in the past 24 weeks
  c) documented history of rectal gonorrhea or chlamydia in the past 24 weeks
- Age ≥ 18 years
- Estimated glomerular filtration rate (GFR) ≥ 60 mL/min according to the Cockcroft-Gault formula for creatinine clearance (CrCl)
- Adequate liver and hematologic function:

  AST and ALT ≤ 2.5 × upper limit of normal (ULN) and total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin

  Absolute neutrophil count ≥ 1000/mm^3; platelets ≥ 75,000/mm^3; hemoglobin ≥ 10 g/dL
- No suspected or known active, serious infection(s)
- No evidence of acute viral hepatitis A, B or C, or evidence of chronic hepatitis B virus infection. Subjects found to be susceptible to HBV infection should be referred for HBV vaccination. Subjects found to be positive for HCV must not have active infection or must have completed treatment and achieved a sustained virologic response
- Have not received investigational agents for the treatment or prevention of HIV-1 infection in the 30 days prior to screening
- No history of osteoporosis or bone fragility fractures

Study Periods / Phases

Subjects will be treated for at least 96 weeks during the blinded treatment phase. After completing the Week 96 visit, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the last subject reaches Week 96. All subjects will return to the study center for an End of Blinded Treatment Phase visit (may coincide with their next scheduled visit) upon notification by Gilead. Subjects who are still on study drug and subjects who have discontinued study drug due to HIV infection at the End of Blinded Treatment Phase visit will be offered entry into the 48 week OL phase of the study.

All subjects participating in the OL extension phase, without regard to their blinded treatment regimen, will be administered F/TAF QD and return for study visits at OL Weeks 12, 24, 36 and 48. HIV infected subjects may continue participation in the OL phase but will not be offered OL F/TAF.

In geographic regions where F/TAF is commercially available for PrEP, subjects will discontinue study drug at OL Week 48 and return 30 days later for a 30-Day Follow-Up visit. In geographic regions where F/TAF is not yet commercially available for PrEP, subjects will be given the option to continue receiving OL F/TAF beyond OL Week 48 and attend visits every 12 weeks until F/TAF becomes commercially available for use as PrEP, or until Gilead Sciences terminates the clinical development of F/TAF for PrEP (except in Denmark and the United Kingdom).

During the blinded treatment phase, subjects may choose to continue to participate in the study without taking study drug ("on-study, off-study drug"). Subjects who permanently discontinue study drug and continue to attend normal study visits (at minimum one visit at least 30 days after last dose) are not required to complete the follow-up visit. Any subject who has an Early Study Drug Discontinuation (ESDD) visit and who will not continue participating in the study, or any subject who will not continue participation in the OL phase of the study, must complete the 30-Day Follow-Up visit 30 days after the last dose of study drug.

Schedule of Assessments

After screening procedures, eligible subjects are randomized 1:1 to F/TAF or F/TDF and treated for 96 weeks. Following the Day 1 visit, subjects will be required to return for study visits at Weeks 4 and 12, and then every 12 weeks thereafter. All subjects will return to the clinic for an End of Blinded Treatment Phase visit (may coincide with their next scheduled visit) upon notification by Gilead.

For all eligible subjects, blood is 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), sexually transmitted infection (STI) testing for syphilis (blood), gonorrhea and chlamydia (pharyngeal, rectal [except Week 4], urine), HIV testing (Covance central laboratory tests of HIV-1 Ab/Ag and local tests of 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab), DBS (starting at Week 4), and complete or symptom directed physical examinations are performed at Screening, Week 4 and all subsequent visits. In addition, HIV-1 RNA by PCR test is collected for subjects who (1) have a positive retest rapid HIV-1 Ab/Ag test, (2) have a positive HIV-1 Ab/Ag test, (3) show symptoms consistent with acute infection regardless of the results of the rapid tests, (4) have a recent exposure that is considered high risk for HIV infection or (5) have been confirmed to be HIV infected.

At Day 1, local tests of 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab and symptom directed physical examinations are performed. At Screening or Day 1, if the subject has a negative rapid test, but has signs or symptoms of acute HIV-1 infection, an HIV-1 RNA by PCR test will be completed and if HIV-1 RNA by PCR is positive, subject cannot participate in the study.

Testing is done for HBV every 24 weeks and HCV every 48 weeks.

Urine is collected for evaluations of renal function including urine creatinine, urine protein, retinol binding protein (RBP), and beta-2 microglobulin.

Questionnaires assessing HIV risk behavior were collected at screening, Day 1 and all visits (excluding 30-day follow-up) for the Computer-Assisted Self-Interview (CASI) and at screening for the Alcohol Use Disorders Identification Test (AUDIT).

Adverse events and concomitant medications are assessed at each visit.

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

More details for study procedures could be found in Appendix 1.

Pharmacokinetics

A trough PK blood sample for plasma and PBMC PK analyses is obtained approximately 24 hours after the last dose of study drug and prior to administration of study drug the day of the visit (Week 4 only). Anytime PK blood samples are obtained at all visits after Week 4 except for the 30-day follow-up visit until subjects discontinue study drug.

Week 4 trough PK, Week 4 trough PBMC PK, anytime PK, and DBS analyses will be conducted in a subset (10%) of subjects. On 16 December 2016, a random sampling of 10% of the enrolling subject numbers was selected for these analyses. During the study randomization treatment assignments conducted by IWRS, subjects receive 4-digit subject identification numbers sequentially assigned by randomization order, ranging from 2000 to 7999 (including 1000 extra subject identification numbers for possible over enrollment). Using these pre-specified subject identification numbers, a randomization ratio of 1:9 for PK/PBMC PK analyses vs. no PK/PBMC PK analyses, a block size of 10, and 600 blocks, 10% of enrolled subjects were randomly selected for analyses. DBS samples and anytime PK will be analyzed for all subjects diagnosed with HIV infection (cases) and subjects selected as matched controls to HIV infected subjects (ratio of 5 controls to each HIV infection case) as described in Appendix 9. In addition, Week 4 trough PK and Week 4 trough PBMC PK may be analyzed for subjects diagnosed with HIV infection.

Randomization

Subjects are randomized in a 1:1 ratio to 1 of 2 Treatment Groups (Treatment Group 1: Treatment Group 2).

Site and/or Stratum Enrollment Limits

Ninety-four investigative sites in 68 cities across 11 North American and European countries enrolled subjects. There was no prespecified enrollment limit for individual sites.

Study Duration

The randomized, double-blind phase of this study is at least 96 weeks in duration. The open-label extension phase of this study is at least 48 weeks in duration.

1.3. Sample Size and Power

1.3.1. Sample Size and Power (Protocol Pre-specified)

A sample size of 2500 in each arm (1:1 randomization) provides at least 82% power to show F/TAF is non-inferior to F/TDF with respect to the HIV-1 infection rate. In this power analysis, a HIV-1 infection rate of 1.44 per 100 person-years (PY) in the F/TAF and F/TDF treatment arms, a 2-sided Type 1 error rate of 5%, a non-inferiority margin of 1.62, and an average follow-up of 2 years (ie, last subject has a minimum of 48 weeks of follow-up and at least 50% of the subjects have at least 96 weeks of follow-up after randomization) are assumed.

The non-inferiority (NI) margin of 1.62 and HIV infection rate of 1.44 per 100 PY are based on an equal weighting approach using three historical studies of F/TDF versus placebo/untreated arms in MSM populations that are very similar to the population intended for this study (see Table 1-1 below; the NI margin of 1.62 per 100 PY is the square-root of the lower bound of the 95% CI (2.64) of rate ratio to preserve 50% of treatment effect). The largest of the three studies is the iPrEX study and the unprotected receptive anal intercourse (URAI) subgroup of the iPrEX study is a high-risk population similar to the intended population of this study. Equal weighting for the three studies gives relatively more weight to the two smaller contemporary studies (PROUD and IPERGAY) than the alternative method of inverse variance weighting, thus providing an estimate that is likely to be closer to the true estimate of F/TDF efficacy for PrEP. PROUD and IPERGAY were conducted when F/TDF was already established as an effective PrEP medication and represent the status for subjects in the proposed study. iPrEX, the largest and earliest of these three studies, was conducted when the effectiveness of F/TDF for PrEP was not established; thus, participants were informed of the unproven efficacy of F/TDF, which likely contributed to the much lower adherence rate in the iPrEX trial. In contrast, PROUD and IPERGAY are more recent studies and were conducted after F/TDF was approved for prevention of HIV in a similar risk population, which likely contributed to the much higher adherence rate reported.

Table 1-1. Efficacy Information from Truvada as PrEP in MSMs

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

Source: iPrEX from {Grant 2010}; IPERGAY from {Molina 2015}; PROUD from {McCormack 2015}
* The pooled incidence rate for placebo and F/TDF, based on equal weighting of three studies, are within {} which are used for estimating the rate ratio and its 95% CI.

The DXA substudy with 400 subjects (200 in each treatment group) will provide at least 95% power to detect 1.54% difference between F/TAF and F/TDF treatment groups in terms of percentage change from baseline to Week 48 in BMD. In this power assessment, it is assumed that the standard deviation for percent change in BMD is 3.05% and 3.15% in the F/TAF and F/TDF treatment groups, respectively and 2-sided t-test will be conducted at a 0.01 level. The mean differences and standard deviations are based on GENVOYA (GEN) Studies GS-US-292-0104/GS-US-292-0111 (E/C/F/TAF vs E/C/F/TDF) and VEMLIDY (VEM) HBV Studies GS-US-320-0108/GS-US-320-0110 (TAF vs TDF). To be conservative, the smallest effect size from spine in HIV studies was used for the estimation of mean difference and standard deviation between the 2 treatments in the sample size calculation.

For the percent change in renal biomarkers of urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio from baseline to Week 48, the sample size of 2500 in each arm will have at least 95% power, given the probability of a subject from F/TAF is less than that from F/TDF, P(F/TAF < F/TDF), is at least 55% using a 2-sided Wilcoxon rank sum test at 0.02 level.

The sample size of 2500 in each arm will also provide at least 95% power to demonstrate that F/TAF has 0.014 mg/dL less increase at Week 48 in serum creatinine than F/TDF, assuming the standard deviation is 0.114 and 0.097 in F/TAF and F/TDF, respectively, and 2-sided t-test will be conducted at 0.02 level. The mean differences and standard deviations are based on GEN HIV Studies GS-US-292-0104/GS-US-292-0111 (E/C/F/TAF vs E/C/F/TDF) and VEM HBV Studies GS-US-320-0108/GS-US-320-0110 (TAF vs TDF). To be conservative, the smaller effect size from VEM HBV Studies GS-US-320-0108/GS-US-320-0110 was used for the estimation of mean difference and standard deviation between the 2 treatments in the sample size calculation.

The above power calculations for BMD and renal biomarkers are based on historical data from studies where subjects take study drug daily; if subjects are less than fully adherent, the observed benefit of F/TAF compared to F/TDF will be less than these historical estimates, and thus the above power calculation may be overly optimistic.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

An external multidisciplinary Independent Data Monitoring Committee (IDMC) reviews the progress of the study and performs interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the IDMC may recommend to the sponsor whether the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications. Interim efficacy results were also provided to the IDMC for review.

The Week 24 Independent Data Monitoring Committee (IDMC) analysis has been conducted after approximately the first 50% of enrolled subjects completed their Week 24 visit or prematurely discontinued the study drug.

The Week 48 IDMC analysis has been conducted after approximately the first 50% of enrolled subjects completed their Week 48 visit or prematurely discontinued the study drug.

The Week 72 IDMC analysis has been conducted after approximately the first 50% of enrolled subjects completed their Week 72 visit or prematurely discontinued from the study drug.

The IDMC's role and responsibilities and the scope of analysis to be provided to the IDMC are provided in a mutually agreed upon charter, which defines the IDMC membership, meeting logistics, and meeting frequency.

No formal interim efficacy analysis, which may lead to early termination for efficacy or futility, is planned.

2.2. Primary Analysis

The primary analysis was conducted after all subjects have a minimum follow-up of 48 weeks and at least 50% of the subjects have 96 weeks of follow-up after randomization or prematurely discontinue from the study.

2.3. End of Blinded Treatment Phase Analysis

The end of blinded treatment phase analysis was conducted after all subjects have completed the end of blinded treatment visits or prematurely discontinue from the study.

This SAP describes the analysis plan for the end of blinded treatment phase analysis.

2.4. Final Analysis

The final statistical analysis will be conducted after all subjects either complete the study or prematurely discontinue from the study.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The end of blinded treatment phase analysis will include all data collected from the randomized and the open-label extension (OLE) phase of the study. Only data collected in the double-blinded (DB) phase (ie, DB phase data) will be summarized, if not specified otherwise. Data collected from both phases will be included in data listings.

A subject is considered to have enrolled in the open-label extension if the entry of OLENTRY form is 'yes'. The cutoff date of the OLE phase will be the date of first dose date of the OLE phase if it is available. If the subject is never dosed in the OLE phase, all available data are considered as the DB phase data.

For subjects who are not enrolled in the OLE phase, all available data are considered as the DB phase data. For subjects who are treated in the OLE phase, data collected up to the cutoff date will be considered as DB phase data, and data collected after the cutoff date will be considered as OLE phase data, except for adverse events (AEs), concomitant medications, and death. For AEs, concomitant medications, and death, data collected prior to the cutoff date are considered as DB phase data, and data collected on or after the cutoff date is considered OLE phase data.

Analysis results will be presented using descriptive statistics. In general for categorical (or ordinal) variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

By-subject listings will be presented for all subjects in the All Randomized Analysis Set and sorted by subject ID number, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within a subject. The treatment group to which subjects were randomized will be used in the listings. Age, MSM/TGW status, race, first dose date and HIV infection date will be included in the listings, as space permits.

In general, permanent discontinuation of study drug refers to premature discontinuation of study drug or completion of study drug and regardless of any gaps in continuous dosing (ie, temporary discontinuation due to adverse event (AE) or subject request after which subjects may resume study drug).

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The rules for inclusion of subjects in each analysis set will be determined before the study blind is broken for analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

3.1.1. All Randomized Analysis Set

The **All Randomized Analysis Set** will include all subjects who are randomized into the study. This is the primary analysis set for by-subject listings.

3.1.2. Full Analysis Set

The **Full Analysis Set (FAS)** will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, (3) are not HIV positive on Day 1 (defined as subjects with either a) negative Covance antibody test results at first post baseline assessment or b) negative local lab Day 1 rapid test), and (4) in order to contribute to the efficacy analyses of HIV infection, should have at least one post-baseline HIV laboratory assessment (from either local or central laboratory).

Of note, negative Covance antibody test results are defined as either (1) a negative HIV Screening antibody test result or (2) a positive Screening antibody test plus a negative discrimination antibody test result. Subjects will be grouped according to the treatment to which they were randomized.

The FAS is the primary analysis set for efficacy analyses.

3.1.3. Per Protocol Analysis Set

The **Per Protocol (PP) Analysis Set** will consist of all subjects in the FAS excluding those with any of the major protocol violations listed below. Subjects will be grouped according to the treatment they actually received. The PP analysis set will be used for an on study drug PrEP treatment (on-treatment) HIV infection sensitivity analyses of the primary endpoint.

PP analysis set will exclude (from FAS) subjects meeting any of the following criteria:

- Subjects where evidence suggests that they have pre-existing HIV that was contracted prior to first dose date of study drug (defined as subjects for whom HIV infection prior to first dose date of study drug cannot be excluded as the subjects did not have a Covance HIV antibody or HIV-1 RNA test analyzed between first dose date (inclusive) and prior to the date of diagnosis of HIV infection) based on Gilead's evaluation

- Subjects vaccinated for HIV (identified from the Medical History eCRF or Non-Study ARV Medication eCRF)

- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the table in protocol Section 5.4 including drugs not to be used with FTC and TAF

3.1.4. Safety Analysis Set

The **Safety Analysis Set** will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of study drug.

Subjects will be grouped according to the treatment they actually received. This is the primary analysis set for safety analyses.

3.1.5. DXA Analysis Sets

3.1.5.1. Hip DXA Analysis Set

The **Hip DXA Analysis Set** will include all subjects who (1) are in the Safety Analysis Set and (2) have nonmissing baseline hip BMD values. Subjects will be grouped according to the treatment they actually received.

3.1.5.2. Spine DXA Analysis Set

The **Spine DXA Analysis Set** will include all subjects who (1) are in the Safety Analysis Set and (2) have nonmissing baseline spine BMD values. Subjects will be grouped according to the treatment they actually received.

3.1.6. Pharmacokinetic Cohort Analysis Set

The **PK Cohort Analysis Set** will include all subjects who (1) are in the Safety Analysis Set, (2) are selected in the random sampling of 10% of the enrolled subjects as described in Section 1.2, and (3) have at least 1 nonmissing plasma PK, PBMC PK or DBS concentration value for any analyte of interest reported by the PK lab. The PK Cohort Analysis Set will be used for general PK analyses for the cohort substudy.

3.1.7. Pharmacokinetic Case-Control Analysis Set

The **PK Case-Control Analysis Set** will include all subjects who (1) are in the Safety Analysis Set, (2) have HIV infection or were selected as a matched control for a HIV infected subject, and (3) have at least 1 nonmissing plasma PK, PBMC PK or DBS concentration value for any analyte of interest reported by the PK lab. The PK Case-Control Analysis Set will be used for general PK analyses for the case-control substudy.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set or the FAS, subjects will be grouped according to the treatment to which they were randomized. For other analyses, subjects will be grouped by actual treatment received. The actual treatment received will differ from the randomized treatment only when the actual treatment received differs from randomized treatment for the entire treatment duration.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling subjects. Analyses of BMD, renal safety endpoints, weight and BMI will be adjusted for baseline F/TDF for PrEP.

3.4. Examination of Subject Subgroups

3.4.1. Subject Subgroups for Efficacy Analyses

The HIV infection rate per 100 PY will be analyzed for the following subject subgroups (see Section 6.2.7 for details):

- Age (years): (a) < 25 and (b) ≥ 25
- Race: (a) any black (includes mixed races with any black ancestry) and (b) nonblack
- Ethnicity: (a) Hispanic and (b) Non-Hispanic
- Region: (a) US and (b) Ex-US (Canada and European Union)
- Region: (a) North America (US/Canada) and (b) European Union
- Baseline F/TDF for PrEP medications (a) Yes and (b) No (defined in Section 7.6.3)
- Screening HIV risk characteristics, from CASI screening questionnaire
- Highest level of education: (a) < 4 year college (ie. Less than high school, High school/GED, Some college, 2-year college/AA, Other) and (b) ≥ 4 year college (ie. 4-year college, Master's degree, Doctoral degree, Professional degree)
- Circumcised: (a) Yes and (b) No
- Recreational drug use in the last 3 months prior to Screening: (a) Yes and (b) No
- URAI partners in the last 90 days prior to Screening: (a) ≤ 3 URAI partners and (b) > 3 URAI partners
- Screening HIV risk characteristics, from AUDIT screening questionnaire
- Six or more drinks on one occasion (a) Never or frequency of alcohol use never and (b) Yes (includes Less than monthly, Monthly, Weekly, Daily or almost daily)
- Any history of rectal gonorrhea, rectal chlamydia or syphilis STI in the past 24 weeks from Medical History eCRF: (a) Yes and (b) No

3.4.2. Subject Subgroups for Safety Analyses

Selected bone safety endpoints may be analyzed for the following subject subgroups (see Section 7.3.1.1 for details):

- Baseline F/TDF for PrEP medications (a) Yes and (b) No (defined in Section 7.6.3)

Selected renal safety endpoints may be analyzed for the following subject subgroups (see Sections 7.4.3.1 and 7.4.5.1 for details):

- Baseline F/TDF for PrEP medications (a) Yes and (b) No (defined in Section 7.6.3)

Selected renal biomarker ratios and fasting metabolic assessments may be analyzed for the following subject subgroups (see Sections 7.4.1.1 and 7.4.2.1 and 7.2.3.1 for details):

- Baseline F/TDF for PrEP medications (a) Yes and (b) No (defined in Section 7.6.3)

3.5. Multiple Comparisons

The noninferiority evaluation of the incidence of HIV infection per 100 PY when all subjects have a minimum follow-up of 48 weeks and at least 50% of the subjects have 96 weeks of follow-up after randomization is the prespecified primary comparison. However, 3 interim IDMC analyses prior to the analysis for the primary endpoint have been 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% confidence interval [CI]) using the FAS. No alpha level adjustment is applied for the analysis at the end of blinded phase.

3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing datum for a given study analysis window may be due to any of the following reasons:

- A visit occurring in the window but data were not collected or were unusable
- A visit not occurring in the window
- A subject prematurely discontinuing from the study before reaching the window

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For the secondary endpoints of the percent changes from baseline in hip BMD and spine BMD in a subset of subjects, urine beta-2-microglobulin to creatinine ratio, and urine RBP to creatinine ratio, the distribution of UP and UPCR categories and the change from baseline in serum creatinine, missing values will be imputed using the last observation carried forward (LOCF) method and baseline observation carried forward (BlOCF) method.

The algorithm for LOCF is as follows:

- If a postbaseline value is missing in an analysis visit window, the missing value will be replaced with the last on-treatment value (ie, data collected up to 30 days after permanent discontinuation of study drug or all available data for subjects who were still on study drug) observed before the analysis visit window that has the missing value.

- Baseline values will be carried forward to impute the postbaseline value at a specific visit, if there is no nonmissing postbaseline observation collected prior to that visit.

The algorithm for BlOCF is as follows:

- Baseline values will be carried forward to impute the missing postbaseline value at a specific visit.

For missing or incomplete last dosing date of study drug, imputation rules are described in Section 3.8.1. For missing or incomplete start or end dates of study drug for the computation of study drug interruptions, imputation rules are described in Section 4.2.2.2. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.6. Imputation rules for missing DBS concentration at the time of HIV diagnosis are as described in Appendix 9.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process. No prespecified sensitivity analyses to evaluate the impact of outliers are planned. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. If a randomized subject was not dosed with any study drug, the randomization date will be used instead of the first dosing date of study drug. For screen failures, the date the informed consent was signed will be used for age calculation. If only the birth year is collected on the CRF, “01 July” will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, “01” will be used for the unknown birth day.

Laboratory data (non-PK) that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows except for urine creatinine:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 or < 5.0, values of 49 or 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

For urine creatinine, a value of "< 1" is handled as a missing value in its summary and the calculation of related ratios.

HIV-1 RNA results of 'No HIV-1 RNA detected' and "<20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purposes. HBV DNA results of "<20 IU/mL HBV DNA detected" or "No HBV DNA detected" will be imputed as 19 IU/mL for analysis purposes. HCV RNA results of "<15 IU/mL HCV RNA detected" or "No HCV RNA detected" will be imputed as 14 IU/mL for analysis purposes.

Natural logarithmic transformations will be used for analyzing PK and PBMC trough concentrations. Concentration values that are below the lower limit of quantitation (BLQ) will be presented as "BLQ" in the concentration listing. Trough PK, trough PBMC and DBS RBC concentration values that are BLQ will be treated as one-half of the lower LOQ.

The following conventions will be used for the presentation of summary and order statistics for PK and PBMC concentrations:

- If at least 1 subject has a concentration data value of BLQ for the time point, the minimum value will be displayed as "BLQ".

- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ".

- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ".

- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ".
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) and summary statistics will be displayed as "BLQ".

3.8. Analysis Windows

3.8.1. Definition of Study Day

Study Day 1 (DB phase) is defined as the day when the first dose of randomized study drug (ie, *F/TAF or Placebo-to-match F/TAF*, *F/TDF or Placebo -to-match F/TDF*) was taken, as recorded on the Study Drug Administration eCRF form.

Study Day 1 (OLE phase). For subjects who were treated in the OLE phase, Study Day 1 is defined as the day when the first dose of OLE phase study drug (ie, *F/TAF)* was taken, as recorded on the "Extension Phase" Study Drug Administration eCRF.

Study Days are calculated relative to Study Day 1 for each phase. For events that occurred on or after the Study Day 1 date, the number of study days is calculated as (visit date minus Study Day 1 date plus 1). For events that occurred prior to DB phase Study Day 1, the number of study days is calculated as (visit date minus Study Day 1 date).

Last Dose Date (DB phase) is the latest of the blinded study drug end dates (administering ≥1 tablet per day) recorded on the Study Drug Administration eCRF form with "Permanently Withdrawn" box checked for subjects who prematurely discontinued or completed study drug in the blinded treatment study phase according to the Study Drug Completion eCRF.

If last dose date is completely missing (ie, due to lost to follow-up) for subjects who prematurely discontinued or completed blinded study drug at the data cut date in the DB phase, the latest of study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding the date of 30-day follow-up visit, from the DB phase data, will be used to impute the DB phase last dose date. For other partial missing last dose date, please see the programming specifications for imputation rule details.

If the DB phase last dose date is after the first dose date of the OLE phase, use the day before the first dose date of the OLE phase to impute it.

Last Dose Date (OLE phase) is defined as the latest of the OLE phase study drug end dates recorded on the "Extension Phase" Study Drug Administration eCRF with "Permanently Withdrawn" box checked for subjects who prematurely discontinued study drug according to the "Extension Phase" Study Drug Completion eCRF. This date will only be available for subjects treated in the OLE phase of the study. If the last dose date is missing for subjects who prematurely discontinued study drug in the OLE phase of the study, the latest of nonmissing OLE phase study drug start dates and end dates, the clinical visit dates, and the laboratory visit dates, excluding the date of 30-day follow-up visit, from the OLE phase data, will be used to impute the OLE phase last dose date.

Last Study Date is the latest of the randomized or OLE phase (if available) study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for subjects who prematurely discontinued study or who completed study according to the Study Completion eCRF.

Last At-Risk of HIV Infection Date (DB phase) is (1) the date of HIV infection diagnosis as defined in Section 6.2.2 for subjects who have been diagnosed as infected with HIV during the DB phase or (2) the date of the last post-baseline HIV laboratory test (either local rapid or Covance HIV laboratory tests, including the 30-day follow-up visit date) during the DB phase for subjects who have not been infected with HIV during the DB phase.

Last At-Risk of HIV Infection Date (OLE phase) is (1) the date of HIV infection diagnosis as defined in Section 6.2.2 for subjects who have been diagnosed as infected with HIV during the OLE phase or (2) the date of the last post-baseline HIV laboratory test (either local rapid or Covance HIV laboratory tests, including the 30-day follow-up visit date) during the OLE phase for subjects who have not been infected with HIV.

Baseline value is defined as the last value obtained on or prior to Study Day 1 for each phase for all assessments, except for DXA BMD. The baseline value for DXA BMD is defined as the last value obtained on or prior to Study Day 14 of each phase.

3.8.2. Analysis Windows

Subject visits might not occur on protocol specified days. Therefore, for the purpose of analysis, observations collected from the DB phase of the study (ie, DB phase data) will be assigned to analysis window. Observations collected from the OLE phase of the study (ie, OLE phase data) will not have analysis window assigned and will be included in listings with derived visit marked as “Extension”.

The CASI questionnaire assessment consists of different versions of the questionnaire corresponding to 3 different time periods: screening, baseline and follow-up. All versions of the CASI questionnaire include questions regarding number of sexual partners. For the CASI Screening questionnaire items regarding the number of sexual partners in the last 90 days, the analysis windows are defined as prior to the first dose date. For the CASI Baseline questionnaire items, the analysis windows are defined up to or on the first dose date.

Aside from the number of sexual partners, other items collected in the CASI Screening questionnaire are unique to the screening questionnaire and collected only once (including education, circumcision, drug use, management of HIV risk, etc.) All of these other CASI Screening questionnaire items will be summarized for the Screening visit without applying an analysis window.

The analysis windows for HIV, hematology, chemistry (including glucose), urinalysis, renal biomarkers, $eGFR_{CG}$, vital signs, weight, CASI Follow-Up questionnaire, and DBS are presented in Table 3-1.

Table 3-1. Analysis Windows for HIV, Hematology, Chemistry, Urinalysis, Renal Biomarkers, eGFR$_{CG}$, Vital Signs, Weight, CASI Follow-Up Questionnaire, and DBS

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week 108	756	715	798
Week 120	840	799	882
Week K (K is every 12 weeks after previous visit)	K*7	(K-6)*7+1	(K+6)*7

HIV laboratory tests include both Covance central laboratory tests (HIV antibody screening tests, HIV Antibody Supplemental tests, qualitative and quantitative tests) and local laboratory tests (rapid HIV 1 Ag/Ab test or other local laboratory tests collected from eCRFs).
CASI follow up questionnaire collected at post baseline visits only, no baseline analysis window will be applied.

The analysis windows for fasting glucose, lipids (including total cholesterol, high density lipoprotein [HDL], direct low density lipoprotein [LDL], and triglycerides), HBV serology (including HBsAb, HBsAg, and HBcAb) and HBV DNA assessments are presented in Table 3-2.

Table 3-2. Analysis Windows for Fasting Glucose, Lipids, HBV Serology and HBV DNA Assessments

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	168	2	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756
Week 120	840	757	924
Week K (K is every 24 weeks after previous visit)	K*7	(K-12)*7+1	(K+12)*7

Fasting glucose and lipids (fasting not required at screening) include total cholesterol, HDL, total cholesterol to HDL ratio, direct LDL, and triglycerides from Covance central laboratory data.

The analysis windows for anytime PK, STI laboratory tests for gonorrhea, chlamydia and syphilis as well as syphilis diagnosis by the investigator are presented in Table 3-3.

Table 3-3. Analysis Windows for Anytime PK, STI Laboratory Tests and Syphilis Diagnosis by the Investigator

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	84	2	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week 108	756	715	798
Week 120	840	799	882
Week K (K is every 12 weeks after previous visit)	K*7	(K 6)*7+1	(K+6)*7

STI laboratory tests include Covance central laboratory tests and local laboratory tests for gonorrhea and chlamydia (urine, rectal swab and pharyngeal swab) as well as syphilis.

The analysis windows for HCV antibody (HCVAb) and HCV RNA are presented in Table 3-4.

Table 3-4. Analysis Windows for HCV Serology and HCV RNA Assessments

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 48	336	2	504
Week 96	672	505	840
Week K (K is every 48 weeks after previous visit)	K*7	(K-24)*7+1	(K+24)*7

The analysis windows for DXA BMD are presented in Table 3-5. Subjects will have a DXA scan at the end of blinded treatment visit, in additional to the regular DXA scans at every 48 weeks, which may result in multiple assessments for a single analysis window. For post Week 144 visit, the value closest to the lower limit of its analysis window will be used for analysis. For other visits, values closest to the nominal visit will be used.

Table 3-5. Analysis Windows for DXA BMD

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	14
Week 48	336	15	504
Week 96	672	505	840
Week 144	1008	841	1176
Post Week 144	(none)	1177	(none)

Note: The baseline value of DXA BMD is defined as the last value obtained on or prior to Study Day 14. For post Week 144, the value closest to the lower limit of its analysis window will be used for analysis.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window. All values will be included in listings, but when a single value is required for analysis and table summarization the selection criteria listed below will apply.

If multiple valid, nonmissing, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the date of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.

  For CASI questionnaires administered for (1) screening and (2) baseline visits, there should not be any instances of multiple screening or baseline records and such instances should be queried.

  - For CASI Baseline questionnaires that still contain multiple records per subject ID after data query, the last record collected on or prior to the first dose date will be selected.

  - For CASI Screening questionnaires that still contain multiple records per subject ID after data query, the last record collected prior to the first dose date will be selected.

  For Alcohol Use Disorders Identification Test (AUDIT) questionnaires collected at screening only, there should not be any instances of multiple baseline records and such instances should be queried. For AUDIT questionnaires that still contain multiple records per subject ID after data query, the last record(s) collected on or prior to the first dose date will be selected.

- For postbaseline visits:

  For BMD data, the record(s) collected on the latest day in the window will be selected for analysis.

  For CASI Follow-Up questionnaires, the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected. Additionally, as some subjects retrospectively completed CASI questionnaires for previous missed visits, when multiple record(s) occur on the same day, the record with a subject assigned visit week equal to the analysis window visit week defined in Section 3.8.2 will be selected.

For Week 4 PK and PBMC trough samples, analysis windows will not be applied, but only samples labeled as a 'trough' collection will be selected. For anytime PK samples, only samples labeled as an 'anytime' collection will be selected and the rules below for other numeric observations applied.

For other numeric observations (ie, except BMD, CASI and Week 4 trough specified above), the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

For any numeric observations, if there are multiple records on the selected day, the average will be taken.

If multiple valid nonmissing categorical measurements exist in a window, records will be chosen as follows:

- For baseline, the last available record on or prior to the first dose date of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (ie, normal will be selected over abnormal) except for gonorrhea and chlamydia laboratory STIs where the worst severity value will be selected (ie, abnormal will be selected over normal).

- For postbaseline visits, the worst severity value within the window will be selected (ie, abnormal will be selected over normal).

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

Subject enrollment has already been summarized in the primary analysis and will not be repeated in this analysis.

4.1.2. Subject Disposition

The summary of subject disposition will be provided by treatment group and overall for all screened subjects. This summary will include the number of subjects screened, screen failure subjects who were not randomized, subjects who met all eligibility criteria and were not randomized, subjects randomized, subjects randomized but never treated, subjects who were HIV positive at screening, subjects in the Safety Analysis Set, and subjects in the FAS, as applicable.

In addition, the number and percentage of the subjects in the following categories will be summarized:

- Still on study drug in the DB phase, if applicable
- Completing study drug in the DB phase
- Prematurely discontinuing study drug in the DB phase (with summary of reasons for discontinuing study drug)
- Still on study in the DB phase, if applicable
- Completing study in the DB phase (see Appendix 11)
- Prematurely discontinuing from study in the DB phase (with summary of reasons for discontinuing study)
- Entering in the OLE phase

The denominator for the percentages of subjects in each category will be the number of subjects in the Safety Analysis Set. Separate summaries of subject disposition in each category by treatment group and overall will include subjects in the Hip or Spine DXA Analysis Sets.

No inferential statistics will be generated. A data listing of reasons for premature study drug/study discontinuation will be provided.

4.2. Extent of Study Drug Exposure and Adherence

4.2.1. Duration of Exposure to Randomized Study Drug

Duration of exposure to study drug will be defined as (the DB phase last dose date the DB phase first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (ie, 4.5 weeks). If subjects have not permanently discontinued study drug (whether still on the randomized study drug or on a study drug interruption) at the time of the data cut date, the latest of study drug start dates and end dates, the clinic visit or laboratory visit dates excluding the 30-day follow-up visit date, will be used to impute the last dose date for the calculation of the duration of study drug exposure.

Duration of exposure to randomized study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum and the total person-years of exposure) and as the number and percentage of subjects exposed for specified periods, ie, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), ≥ 48 weeks (336 days), ≥ 60 weeks (420 days), ≥ 72 weeks (504 days), ≥ 84 weeks (588 days), ≥ 96 weeks (672 days), ≥ 108 weeks (756 days), ≥ 120 weeks (840 days), ≥ 132 weeks (924 days), ≥ 144 weeks (840 days), etc.

Summaries will be provided by treatment group and overall for subjects in the Safety Analysis Set and Hip or Spine DXA Analysis Sets. No inferential statistics will be provided.

Time to premature discontinuation of randomized study drug will be analyzed using the Kaplan-Meier (KM) method by treatment group based on the Safety Analysis Set. The log rank test will be used to compare the difference in time to premature study drug discontinuation between the 2 treatment groups. Subjects who have not prematurely discontinued study drug (whether still on the randomized study drug or on a study drug interruption) at the time of the data cut date will be censored on the imputed last dose date as defined in this section. A plot of KM estimates for the time to premature discontinuation of study drug by treatment group will be generated.

4.2.2. Duration of Study Drug Holidays and Study Drug Interruptions

4.2.2.1. Definition of Study Drug Holidays and Study Drug Interruptions

The duration of study drug holidays and study drug interruptions will only be calculated for the randomize phase study drug. Study drug holidays or other study drug interruptions may occur when subjects cease taking study drug either with or without prior notification to the study sponsor and prior to permanently discontinuing study drug. For subjects who notified the study sponsor of their intention to take a study drug holiday and received pre-approval preceding the end of the interruption, records with ‘0’ tablets administered are entered in the Study Drug Administration eCRF. Other study drug interruptions are defined as gaps in consecutive stop and start dates of study drug records with ≥1 tablet administered in the study drug administration eCRF.

During the DB phase, if subjects are on a study drug holiday or other study drug interruption at the time of the data cut date, the latest of study drug start dates and end dates, the clinic visit or laboratory visit dates during the DB phase, excluding the 30-day follow-up visit date, will be used to impute the end of the interruption for the calculation of the duration of study drug holiday or study drug interruption.

For the DB phase, durations of (1) study drug holidays, (2) other study drug interruptions and (3) any study drug interruptions (the cumulative total of both study drug holidays and other study drug interruptions) will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects with study drug holidays and/or other study drug interruptions for specified periods, ie, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), ≥ 48 weeks (336 days), ≥ 60 weeks (420 days), ≥ 72 weeks (504 days), ≥ 84 weeks (588 days), ≥ 96 weeks (672 days), etc. Multiple study drug holidays and/or interruptions per subject will be combined into one cumulative total duration of study drug holidays and/or interruptions for each subject.

4.2.2.2. Incomplete Dates

If study drug end or restart dates are incomplete (month and year only), then the day for the computation of study drug interruption durations will be imputed as the 15th of the month. However, if the study drug end and restart dates occur in the same month and year and at least one is incomplete (month and year only), then an interruption duration of 15 days will be imputed. If study drug end and restart dates are completely missing or only year is available, data query is needed and no interruption duration will be imputed.

4.2.3. Adherence to Study Drug Regimen

Two measures of study drug regimen adherence will be estimated based on data collected at the site or reported directly by study participants:

1) Prescribed (in-study) pill counts based on pill dispensations and returns on the Study Drug Accountability eCRF,

2) Self-report from CASI questionnaires

Using a randomly selected cohort of study participants, TFV-DP levels in RBCs from DBS analyses (Appendix 9) are planned in order to provide objective data on drug adherence. TFV-DP levels in RBCs from DBS will be analyzed.

4.2.3.1. Adherence to Study Drug Regimen During Study via Pill Counts

For the DB phase, study drug regimen (in-study) prescribed adherence will be computed based on pill counts for active drug only (ie, study drug regimen in Treatment Group 1 includes 1 study drug: *F/TAF active*. Study drug regimen in Treatment Group 2 includes 1 study drug: *F/TDF active*. The numbers of pills of study drug dispensed and returned are captured on the Study Drug Accountability eCRF.

The level of prescribed adherence (or in-study adherence) to the study drug regimen will be determined by the total amount of study drug administered relative to the expected total amount of study drug (1 pill per day for the duration of study participation based on the protocol) and will be calculated from first study drug start date to the end date defined as the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates during the DB phase, excluding the 30-day follow-up visit date. If the subject has been diagnosed with HIV infection during the DB phase, the later date of either the 1) HIV diagnosis date or 2) the DB phase last dose date will be used as the end date. Per study design, subjects that have been diagnosed with HIV infection must immediately discontinue study drug but may remain in the study.

The level of prescribed adherence will be expressed as a percentage using the following formula:

$$Prescribed\ Adherence\ (\%) = \frac{Total\ Amount\ of\ Study\ Drug\ Administered}{Total\ Amount\ of\ Study\ Drug\ Expected\ While\ Participating\ in\ Study} \times 100$$

[1] Total amount of study drug administered is the number of pills dispensed minus the number of pills returned.
[2] Total amount of study drug expected while participating in the study is calculated as the daily number of pills prescribed for the study drug multiplied by the duration of study participation defined as from first dose date to the end date defined as the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding the 30 day follow up visit date. If the subject has been diagnosed with HIV infection, the later date of either the 1) HIV diagnosis date or 2) last dose date will be used as the end date.

If any study drug bottle was not returned, the bottle return status was unknown or the number of pills returned was missing, then it is assumed the number of pills returned was zero. The number of pills taken after the last bottle dispensation visit will be the minimum of 1) the number of pills dispensed minus the number of pills returned (if some bottles were returned) or 2) the number of days between the last bottle dispensation date to the end date as defined in this section. Each subject's adherence rate will be capped at 100%.

Descriptive statistics for overall prescribed adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (ie, < 30%, ≥ 30% to < 60%, ≥ 60% to < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided by treatment group and overall for subjects in the Safety Analysis Set. No inferential statistics will be provided.

4.2.3.2. Adherence to Study Drug Regimen While On-Treatment via Self Report

For the DB phase, adherence to study drug while on-treatment via patient self-report from the CASI follow-up questionnaire data will be summarized by visit from the question: "Approximately how many doses (days) of PrEP tablets have you missed since your last study visit?"

Adherence rates will be calculated based on the number of pills taken divided by the number of days between visits. The number of pills taken is the number of days between visits minus the number of doses (days) of PrEP tablets missed. The number of days between visits is based on 28 days between Day 1 and Week 4, 56 days between Week 4 and Week 12 and 84 days between

visits starting on Week 24 and later. Each subject and visit combinations' minimum adherence rate will be capped at 0%. On-treatment data includes visits occurring through the upper limit of the analysis window corresponding to the date of permanent discontinuation of study drug for subjects that permanently discontinued study drug or all available postbaseline data for subjects who were still on study drug.

By visit descriptive statistics for the adherence rate based on the number of pills missed (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects in adherence categories based on missing the following number of pills (or days) will be summarized.

Table 4-1. Adherence Rates from Number of Doses (Days) of PrEP Tablets Missed in CASI

Adherence rate approximation	Week 4	Week 12	Week 24 and later visits
< 30% adherence	≥ 20 days	≥ 40 days	≥ 59 days
≥ 30% to < 60% adherence	≥ 12 to ≤ 19 days	≥ 23 days to ≤ 39 days	≥ 34 days to ≤ 58 days
≥ 60% to < 80% adherence	≥ 6 to ≤ 11 days	≥ 12 days to ≤ 22 days	≥ 17 days to ≤ 33 days
≥ 80% to < 90% adherence	≥ 3 to ≤ 5 days	≥ 6 to ≤ 11 days	≥ 9 to ≤ 16 days
≥ 90% to < 95% adherence	2 days	≥ 3 to ≤ 5 days	≥ 5 to ≤ 8 days
≥ 95% adherence	≤ 1 day	≤ 2 days	≤ 4 days

Approximate adherence rates are based on 28 pills prescribed for 28 days between Day 1 and Week 4, 56 pills prescribed for 56 days between Week 4 and Week 12 and 84 pills prescribed for 84 days between visits starting on Week 24 and later.

4.3. Protocol Deviations

A summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group and overall based on the Safety Analysis Set. A by-subject listing will be provided for all randomized subjects who violated at least 1 inclusion or exclusion criterion. The listing will include the criteria not met. A listing of subjects who received the wrong study drug will also be provided.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason and the total number of important protocol deviations by deviation reason (ie, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the Full Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of subjects for categorical data. The following summaries of demographic data and baseline subject characteristics will be provided separately for the Safety Analysis Set:

- Age (years)
- Age categories (years): (a) 18 to < 25, (b) ≥ 25 to < 50, (c) ≥ 50
- Sex at birth
- MSM or TGW status
- Race: (a) American Indian or Alaska Native, (b) Asian, (c) Black/Mixed Black, (d) Native Hawaiian or Pacific Islander, (e) White, (f) Other (Nonblack), (g) Not Permitted
- Ethnicity: (a) Hispanic, (b) Non-Hispanic, (c) Not Permitted
- Body weight (kg)
- Height (cm)
- Body mass index [BMI] (kg/m^2)
- Selected self-reported demographic factors from the CASI Screening questionnaire, including:
- Male or Transgender Female status
- Sexuality: (a) Gay/homosexual, (b) Straight/heterosexual (c) Bisexual, (d) Other
- Highest level of education: (a) Less than high school, (b) High school/GED, (c) Some college, (d) 2-year college/AA, (e) 4-year college, (f) Master's degree, (g) Doctoral degree, (h) Professional degree, (i) Other
- Work situation: (a) Full-time employment (employed or self-employed full-time at least 30 hours a week), (b) Part-time employment (employed or self-employed part-time less than 30 hours a week), (c) Part/full time student/education/training, (d) Unemployed, (e) Retired, (f) Other
- Ongoing relationship with a partner: (a) Yes and living with my partner, (b) Yes but not living with my partner, (c) No
- Circumcised: (a) Yes, (b) No, (c) N/A (Post-Operative)

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data or row mean score test for ordinal data) will be used to compare the 2 treatment groups. For weight and BMI, an ANOVA test which includes treatment and baseline F/TDF for PrEP as fixed effects will be used to compare the 2 treatment groups. For other continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

5.2. Baseline Medical Characteristics

Baseline medical characteristics will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of subjects for categorical data. The following summaries of baseline medical characteristics will be provided for the Safety Analysis Set:

- $eGFR_{CG}$ (mL/min)
- HBV infection status (Yes/No/Missing)

  Subjects with HBV infection at baseline are defined as subjects meet any of the following two criteria:

  Positive HBsAg on or prior to the first dose date, or

  Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) on or prior to the first dose date.
- HCV infection status (Yes/No/Not Applicable/Missing)

  Subjects with HCV infection at baseline are defined as subjects with positive HCVAb or quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) on or prior to the first dose date.
- Hip BMD (g/cm^2) for the Hip DXA Analysis Set
- Spine BMD (g/cm^2) for the Spine DXA Analysis Set
- Urine beta-2-microglobulin to creatinine ratio (ug/g)
- Urine RBP to creatinine ratio (ug/g)
- Serum creatinine (mg/dL)
- Proteinuria toxicity grade by urinalysis (dipstick)

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data or row mean score test for ordinal data) will be used to compare the 2 treatment groups. For BMD and serum creatinine, an ANOVA test which includes treatment and baseline F/TDF for PrEP as fixed effects will be used to compare the 2 treatment groups. For renal biomarkers and eGFR, a Van Elteren test stratified by baseline F/TDF for PrEP will be used to compare the 2 treatment groups.

5.3. Baseline HIV Risk Characteristics

Baseline HIV risk characteristics will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of subjects for categorical data. The following summaries of baseline HIV risk characteristics will be provided separately for the Safety Analysis Set:

- Any prior F/TDF for PrEP (defined in Section 7.6.2)
- Baseline F/TDF for PrEP (defined in Section 7.6.3)
- History of syphilis in the past 24 weeks (from Medical History eCRF)
- History of rectal gonorrhea in the past 24 weeks (from Medical History eCRF)
- History of rectal chlamydia in the past 24 weeks (from Medical History eCRF)
- Chlamydia
- Urine (from central laboratory test)
- Rectal (Nucleic acid amplification test [NAAT] or other local laboratory tests)
- Pharyngeal (NAAT or other local laboratory tests)
- Gonorrhea
- Urine (from central laboratory test)
- Rectal (NAAT or other local laboratory tests)
- Pharyngeal (NAAT or other local laboratory tests)
- Syphilis Diagnosis (Yes/No/Missing) from investigator report

  Primary, (b) early latent, (c) secondary, (d) tertiary, (e) late latent, (f) other

  New, (b) re-infection, (c) treatment failure
- Selected Screening visit CASI questionnaire responses to be included are:
- Receptive anal intercourse (RAI) partners in 90 days prior to Screening
- Number of partners
- Percentage of subjects in the categories of: 0, 1, 2, 3, 4-5, 6-10 and ≥ 11 partners

- Unprotected receptive anal intercourse (URAI) partners in 90 days prior to Screening
- Number of partners
- Percentage of subjects in the categories of: 0, 1, 2, 3, 4-5, 6-10 and ≥ 11partners
- Insertive anal intercourse (IAI) partners in 90 days prior to Screening
- Number of partners
- Percentage of subjects in the categories of: 0, 1, 2, 3, 4-5, 6-10 and ≥ 11partners
- Unprotected insertive anal intercourse (UIAI) partners in 90 days prior to Screening
- Number of partners
- Percentage of subjects in the categories of: 0, 1, 2, 3, 4-5, 6-10 and ≥ 11partners
- Recreational drug use in the last 3 months prior to Screening (Yes/No)
- Frequently ask my partner to use a condom for anal sex to manage risk of getting HIV (Yes/No)
- Frequently use condoms to manage risk of getting HIV (Yes/No)
- Prescribed post-exposure prophylaxis for 4 weeks after potential HIV exposure, in the past 12 months prior to Screening
- Number of times prescribed
- Percentage of subjects in the categories of: 0, 1, 2, 3-5, 6-11 and ≥ 12 times prescribed
- AUDIT questionnaire total score at screening (defined in Appendix 5)
- AUDIT questionnaire total score at screening categories (a) < 8 or (b) ≥ 8 to < 15 (c) ≥ 15
- Selected Screening visit AUDIT questionnaire responses to be included are:
- Frequency of alcohol use (a) Never, (b) Monthly or less, (c) 2 to 4 times a month, (d) 2 to 3 times a week, (e) 4 or more times a week
- Alcohol use on days when subject drank (number of drinks): (a) Frequency of alcohol use Never, (b) 1 or 2, (c) 3 or 4, (d) 5 or 6, (e) 7, 8, or 9, (f) 10 or more
- Six or more drinks on one occasion: (a) Frequency of alcohol use Never (b) Never, (c) Less than monthly, (d) Monthly, (e) Weekly, (f) Daily or almost daily
- Felt guilt or remorse after drinking (during the last year): (a) Frequency of alcohol use Never or [Alcohol use on days when subject drank 1 or 2 and Six or more drinks on one occasion Never] (b) Never, (c) Less than monthly, (d) Monthly, (e) Weekly, (f) Daily or almost daily

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data or row mean score test for ordinal data) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

5.4. Medical History

General medical history data will be collected at screening and listed only. General medical history data will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

6. EFFICACY ANALYSES

All necessary summaries on the primary efficacy endpoint (when all subjects have a minimum follow-up of 48 weeks and at least 50% of the subjects have 96 weeks of follow-up after randomization or permanently discontinued from the study) have been performed as part of the Primary Analysis CSR, and will not be repeated for this analysis. Only the DB phase data will be summarized.

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary endpoint is the incidence of HIV-1 infection rate per 100 person-years (PY). The primary endpoint will be assessed when all subjects have a minimum follow-up of 48 weeks and at least 50% of the subjects have 96 weeks of follow-up after randomization or permanently discontinued from the study.

The statistical analysis methods for the primary efficacy endpoint were described in the Primary Analysis SAP and the analysis was performed in the Primary Analysis.

6.2. Secondary Efficacy Endpoint

6.2.1. Definition of the Secondary Efficacy Endpoint

The secondary efficacy endpoint is the incidence of HIV-1 infection rate per 100 person-years (PY) assessed when all subjects have a minimum follow-up of 96 weeks after randomization or permanently discontinued from the study. The HIV-1 infection incidence rate per 100 PY of follow-up will be computed as the number of subjects who became HIV-1 infected during the study after first dose of study drug divided by the sum of all subjects' years (where a year is 365.25 days) of follow-up while at risk of HIV-1 infection during the DB phase study. Follow-up in study while at risk of HIV-1 infection is defined in Section 6.2.3.

6.2.2. Definition of HIV-1 Infection

HIV-1 infection is defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab:

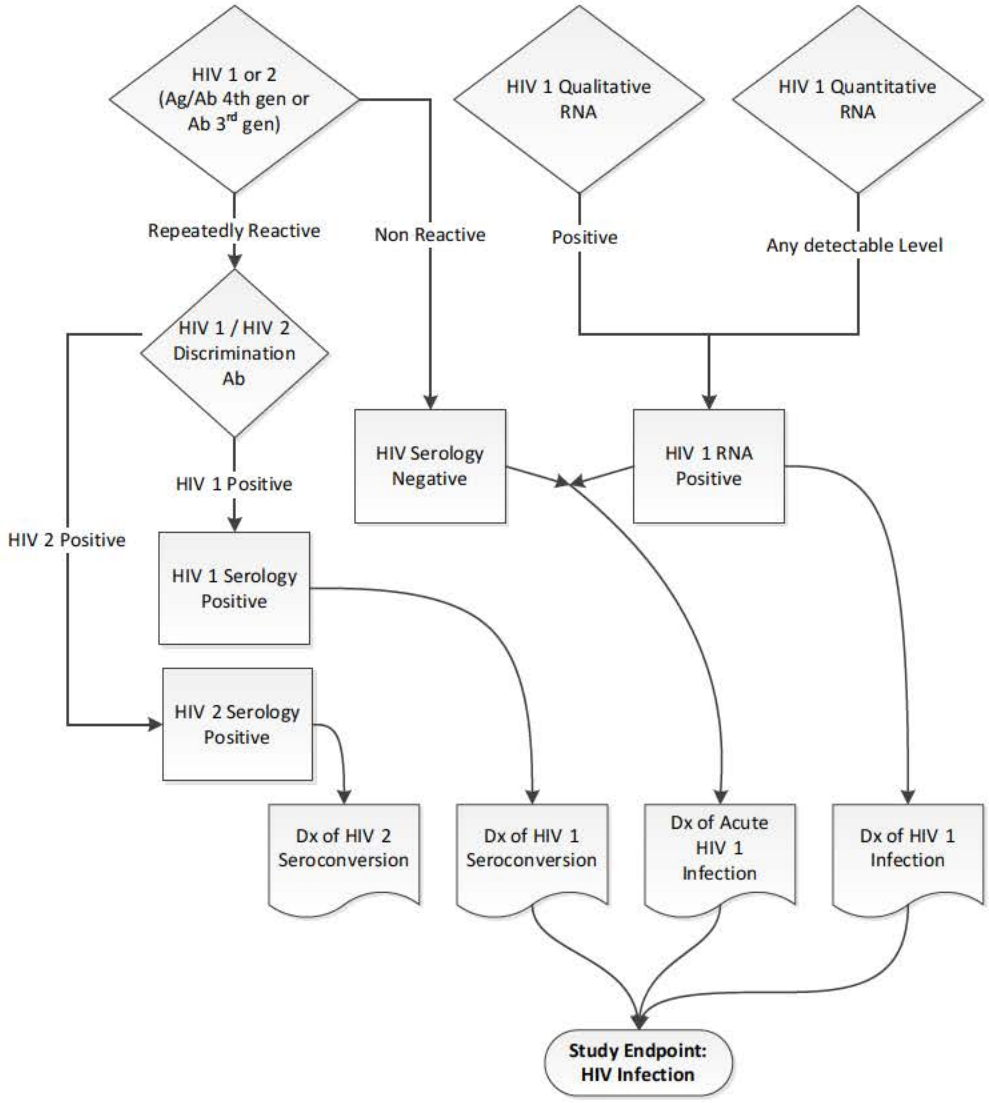
1) Serologic evidence of seroconversion (reactive screening HIV Antigen/Antibody or Antibody test, confirmed by reactive HIV-1/HIV-2 differentiation assay), or

2) Virologic evidence of HIV-1 infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV-1 RNA test), or

3) Evidence of acute HIV-1 infection (reactive p24 Antigen or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Antibody results)

The flowchart in Figure 6-1 focuses on contributions from the central laboratory and provides a general assessment of contributing HIV tests performed by the central laboratory.

Figure 6-1. General Assessment of Contributing HIV tests Performed by the Central Laboratory



Positive virologic evidence, based on qualitative or quantitative HIV-1 RNA tests, is used for confirmation of HIV-1 infection while other HIV tests are also used to assess the date of diagnosis (ie, HIV infection date for analysis).

Positive virologic evidence is defined as either:

1) Qualitative HIV-1 RNA test with positive results or

2) Quantitative HIV-1 RNA test with detectable HIV-1 RNA results ("< 20 cp/ml HIV-1 RNA Detected" or any value ≥ 20 copies/mL)

The date of HIV infection diagnosis is assessed by a retrospective look, starting from the date of the first positive virologic evidence, through the preceding test results from other contributing HIV tests (including both Covance and local tests). The look back stops at the first date with negative assessments on all available HIV tests prior to the date of first positive virologic evidence. The date of HIV-1 diagnosis is set at the earliest positive result in the retrospective look process from either an on-site rapid test, a test sent to the central Covance laboratory, or any other provided local test performed outside of the study that documents the presence of HIV infection.

This algorithm excludes diagnosis of HIV-1 infection for vaccinated subjects who may have positive HIV-1 serology but no positive virologic evidence. For HIV vaccinated subjects, the date of HIV infection diagnosis is the date of first positive virologic evidence, based on qualitative or quantitative HIV-1 RNA tests.

6.2.3. Definition of Duration of At Risk of HIV Infection in Study

Duration of at risk of HIV infection is defined as the time between Day 1 (first dose date) and the end date (end date Day 1 date +1), where end date is defined as the last at-risk of HIV infection date:

1) For subjects who have been diagnosed as infected with HIV during the DB phase: the date of HIV infection diagnosis (as defined in Section 6.2.2)

2) For subjects who have not been infected with HIV during the DB phase: the date of the last post-baseline HIV laboratory test (either local HIV or Covance HIV laboratory tests) during the DB phase (may include the 30-day follow-up visit).

Duration of time at risk of HIV infection in study will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum and total person-years) and as the number and percentage of subjects at risk of HIV infection in study for specified periods, ie, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), ≥ 48 weeks (336 days), ≥ 60 weeks (420 days), ≥ 72 weeks (504 days), ≥ 84 weeks (588 days), ≥ 96 weeks (672 days), ≥ 108 weeks (756 days), ≥ 120 weeks (840 days), ≥ 132 weeks (924 days), ≥ 144 weeks (840 days), etc.

6.2.4. Statistical Hypothesis for the Secondary Efficacy Endpoint

Null hypothesis: The HIV infection rate ratio of F/TAF over F/TDF is at least 1.62 or higher.

Alternative hypothesis: The HIV infection rate ratio of F/TAF over F/TDF is less than 1.62.

6.2.5. Primary Analysis of the Secondary Efficacy Endpoint (HIV Infection Rate Ratio Method)

The analysis purpose of the secondary efficacy endpoint is to assess the noninferiority of treatment with F/TAF relative to treatment with F/TDF via HIV infection rate ratio estimation from a Poisson regression model. Noninferiority will be assessed using a 95% CI constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect and a noninferiority margin of 1.62.

It will be concluded that F/TAF is noninferior to F/TDF if the upper bound of the 2-sided 95% CI of the rate ratio (F/TAF group over F/TDF group) of the HIV infection incidence rate is less than 1.62 (Appendix 2).

If noninferiority of F/TAF versus F/TDF is established, the same 95% CI used in evaluating noninferiority will be used to evaluate superiority. If the upper bound of the 95% CI is less than 1, then superiority of F/TAF over F/TDF using the rate ratio estimation is established. The p-value from a Poisson model will also be used to assess superiority as a secondary assessment. The FAS will be used for the secondary efficacy endpoint analysis and the superiority evaluation.

6.2.6. Sensitivity Analyses of the Secondary Efficacy Endpoint While On-Treatment (HIV Infection Rate Ratio Method)

A sensitivity analysis of the secondary endpoint will be based on HIV infections occurring while subjects are on-treatment during the double-blinded phase of the study using the PP analysis set. This on-treatment analysis will include HIV infection events and follow-up times occurring between first dose date to DB phase last dose date plus 10 days (for F/TDF) or plus 16 days (for F/TAF) and exclude:

1) HIV-1 infection events and follow-up time during the OLE phase.

2) Off study drug PrEP (off-treatment) HIV infection events and follow-up time defined as events and follow-up time occurring greater than 10 days for (F/TDF) or 16 days (for F/TAF) after permanent discontinuation of study drug (Appendix 7).

3) HIV infections and follow-up time occurring after subjects initiated any non-study PrEP treatment that includes the period after permanent discontinuation of study drug (including commercial drugs like Truvada®, generic Truvada, or investigational drugs like cabotegravir for PrEP with a stop date that is either ongoing or after permanent discontinuation of study drug).

The HIV infection incidence rate per 100 person-years of follow-up will be computed as the number of subjects with on-treatment HIV infection divided by the sum of all subjects' years (where a year is 365.25 days) of on-treatment follow-up while at risk of HIV infection in study. The duration of on-treatment follow-up while at risk of HIV infection is defined as the time between Day 1 (first dose date) and the end date (end date Day 1 date +1) where end date is defined as:

1) For subjects who have been diagnosed as infected with HIV while on-treatment: the date of the on-treatment HIV infection which will be the date of the HIV infection diagnosis (as defined in Section 6.2.2).

2) For subjects who have not been infected with HIV while on-treatment, the earlier of:

   a) last dose date + 10 days for F/TDF or + 16 days for F/TAF for subjects who permanently discontinued study drug (including subjects with off-treatment HIV infection)

   b) date of last post-baseline HIV laboratory test (either local or Covance HIV laboratory tests, which may include the 30-day follow-up visit date) for subjects who have not permanently discontinued study drug

   c) start date of any non-study PrEP treatment that includes the period after permanent discontinuation of study drug (including commercial drugs like Truvada, generic Truvada, or investigational drugs like cabotegravir for PrEP with a stop date that is either ongoing or after permanent discontinuation of study drug)

   d) the first dose date of the OLE phase if available.

6.2.7. Subgroup Analysis of the Secondary Efficacy Endpoint

The analysis of the incidence of HIV-1 infection rate per 100 PY will be performed within each subgroup specified in Section 3.4 based on the FAS (Appendix 2).

For each level of the subgroup factors, the incidence rates within each treatment group and 95% CIs will be computed using the exact CIs for the single Poisson rate parameter approach as described for the rate differences method in Section 6.2.8.1.

6.2.8. Exploratory Analysis of the Secondary Efficacy Endpoint

CCI [redacted]

CCI [redacted]

6.3. Changes From Protocol-Specified Efficacy Analyses

The adherence criteria (excluding non-adherent to study drug subjects) is not required for the PP analysis set. For HIV prevention, a lower adherence rate is associated with an increased risk of HIV infection events and thus increased statistical power for evaluation of the HIV infection rate.

7. SAFETY ANALYSES

Safety data from the DB phase will be summarized for the subjects in the Safety Analysis Set. All safety data collected up to 30 days after permanent discontinuation of DB phase study drug and all available data for subjects who were still on study drug or on a study drug interruption will be summarized by treatment group, unless specified otherwise. All safety data will be included in data listings.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life-threatening) according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be left as "missing" for data listings.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE eCRF to the question of "Related to Study Treatment." Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology (PVE) Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs 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
- Any AEs leading to premature discontinuation of study drug.

The TEAE definitions will be applied to the DB phase data and the OLE phase data, separately. When DB phase data are used, AEs onset date will be compared with the DB phase first dose date and last dose date and premature discontinuation of study drug refers to study drug discontinuation in the DB phase. An AE meeting the TEAE criteria will be considered as a TEAE in the DB phase. When OLE phase data are used, AEs onset date will be compared with the OLE phase first dose date and last dose date and premature discontinuation of study drug refers to study drug discontinuation in the OLE phase. An AE meeting the TEAE criteria will be considered as a TEAE in the OLE phase.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent for the DB phase if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The month and year (or year) of the AE onset is the same as or before the month and year (or year) of the date corresponding to the minimum of

    30 days after the date of the DB phase last dose of study drug, and

    the OLE phase first dose date minus 1 day.

The event is considered treatment emergent for the OLE phase if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is **after** the month and year (or year) of the first dosing date of OLE phase study drug, and
- The month and year (or year) of the AE onset is **the same as or before** the month and year (or year) of the date corresponding to 30 days after the date of the last dose of OLE phase study drug.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date marked as ongoing or on or after the first dosing date of randomized study drug, will be considered to be treatment emergent for the DB phase. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of the randomized study drug will be considered treatment emergent for the DB phase.

7.1.6. Summaries of Adverse Events and Deaths

The number and percentage of subjects who experienced at least 1 TEAE during the DB phase will be provided and summarized by SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group using the Safety Analysis Set:

- Any Grade 2, 3, or 4 treatment-emergent AEs
- Any Grade 3 or 4 treatment-emergent AEs
- All treatment-emergent study drug-related AEs
- Any Grade 2, 3, or 4 treatment-emergent study drug-related AEs
- Any Grade 3 or 4 treatment-emergent study drug-related AEs
- All treatment-emergent SAEs
- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs that caused premature discontinuation from study drug

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of subjects who experienced the above AEs. Treatment-emergent deaths observed in the DB phase will be also included in this summary.

Treatment-emergent death refers to deaths that occurred between the DB phase first dose date and the DB phase last dose date plus 30 days (inclusive).

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, all treatment-emergent AEs, Grade 3 or 4 treatment-emergent AEs, treatment-emergent study drug-related AEs, Grade 2, 3, or 4 treatment-emergent study drug-related AEs, and treatment-emergent SAEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs
- Grade 3 and 4 AEs

- SAEs
- Study Drug-Related SAEs
- Deaths
- AEs leading to premature discontinuation of study drug

7.2. Laboratory Evaluations

Laboratory data collected during the DB phase of the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately for all data collected from both phases of the study. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window
- Percentage change from baseline to each postbaseline analysis window (if specified)

A baseline laboratory value will be defined as the last nonmissing value obtained on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

Calcium Corrected for Albumin

Calcium corrected for albumin will be calculated and summarized for the study. The following formula will be used when both serum calcium and albumin results for a given blood drawn are available and serum albumin value is < 4.0 g/dL.

- Calcium corrected for albumin (mg/dL) serum calcium (mg/dL) + 0.8 × (4.0 albumin (g/dL))

Toxicity grading for calcium will be applied based on the corrected values.

Estimated GFR

The Cockcroft Gault formula will be used to calculate $eGFR_{CG}$:

- $eGFR_{CG}$ (mL/min) [(140 age (yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72), where weight is total body mass in kilograms, and SCr is serum creatinine.

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

If there is any laboratory toxicity grading scale overlapping with the normal reference ranges (ie, Grade 1 scale overlaps with normal reference ranges), laboratory values that are within the normal range will be Grade 0, except for lipid tests.

For triglycerides, LDL, and cholesterol, the protocol-specified toxicity grading scale is for fasting test values, so nonfasting lipid results (or lipid results without a known fasting status) will not be graded or summarized by toxicity grades.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Only the laboratory abnormalities during the randomize phase will be summarized. Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to 30 days after permanent discontinuation of randomized study drug or the last available date for subjects who were still on study drug or on a study drug interruption during the DB phase at the time of analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent.

Fasting glucose and nonfasting glucose (including glucose results without a known fasting status) are graded based on different grading scales as specified in the protocol. Fasting status was recommended for postbaseline lipids and not required for Screening lipid assessments. For nonfasting glucose (including glucose results without a known fasting status), fasting glucose, fasting total cholesterol, fasting triglycerides and fasting LDL, maximum postbaseline grade, instead of treatment-emergent grade, will be summarized, as fasting status at baseline was approximately half fasting and half nonfasting; therefore, whether an abnormality is treatment-emergent or not cannot be determined for approximately half of the subjects.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities
- Treatment-emergent Grade 2, 3 and 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with any nonmissing postbaseline values up to 30 days after permanent discontinuation of study drug.

A by-subject listing of all laboratory abnormalities and Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order.

7.2.3. Metabolic Laboratory Evaluations

Fasting status was recommended for postbaseline lipids, but not required for Screening lipid assessments. For metabolic assessments, including glucose and the lipid panel (ie, total cholesterol, triglycerides, LDL, HDL, total cholesterol to HDL ratio), only those measurements collected under fasting status will be summarized. P-values comparing the difference between the 2 treatment groups in baseline values and the change from baseline in metabolic assessment will be estimated from a 2-sided Wilcoxon rank sum test.

In addition, the number and percentage of subjects who took lipid modifying medications at study entry and initiated the medications during the study will be provided, respectively, for all subjects and subjects with both baseline and post-baseline fasting status. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using Fisher's exact test.

A lipid modifying medication is defined as a medication with WHO drug class (ATC drug class Level 2) "LIPID MODIFYING AGENTS" and CMDECOD containing the wording of "STATIN".

A sensitivity analysis of the fasting lipid tests will be performed by excluding subjects who took lipid modifying medications at study entry or initiated the medications during the study: baseline values, values at each visit, and changes from baseline at each visit will be summarized by treatment group using descriptive statistics. Baseline and change from baseline at each visit will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test.

Median (Q1, Q3) of change from baseline in fasting metabolic assessments over time will be plotted by treatment group.

7.2.3.1. Subgroup Analysis for Metabolic Laboratory Evaluations

The analysis of baseline, postbaseline, and change from baseline in fasting metabolic assessments will be summarized by treatment group and visit using descriptive statistics within each baseline F/TDF for PrEP medications subgroup specified in Section 3.4.2. Baseline and change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test.

7.2.4. Liver-Related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Alanine aminotransferase (ALT): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- AST or ALT: (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Total bilirubin: (a) > 1 × ULN, (b) > 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN
- AST or ALT > 3 × ULN and total bilirubin: (a) > 1.5 × ULN, (b) > 2 × ULN
- AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN

The summary will include data from all postbaseline visits up to 30 days after permanent discontinuation of study drug or all available data for subjects who were still on study drug (regardless of study drug interruptions). For individual laboratory tests, subjects will be counted once based on the most severe postbaseline value. For both the composite endpoint of AST or ALT and total bilirubin, and the composite endpoint of AST or ALT, total bilirubin, and ALP, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set with nonmissing postbaseline

value of the tests in evaluation at the same postbaseline visit date. Subjects with AST or ALT > 3 × ULN, total bilirubin > 1 x ULN, or ALP > 1.5 x ULN while on-treatment) as well as subjects with treatment-emergent Grade 3 or 4 ALT, AST, ALP, and total bilirubin) will also be listed.

In addition, baseline, postbaseline, and change from baseline in AST, ALT, ALP, and total bilirubin will be summarized by treatment group and visit using descriptive statistics.

7.3. Bone Mineral Density

BMD data will be summarized for the subjects in the hip or spine DXA analysis sets including on-treatment data collected up to 30 days after permanent discontinuation of study drug and all available data for subjects who were still on study drug or on a study drug interruption.

7.3.1. Percentage Change from Baseline in Hip and Spine Bone Mineral Density

Percentage change from baseline in hip and spine BMD at Week 48 using observed on-treatment data are 2 of the 6 key (α-controlled) secondary endpoints.

The percentage change from baseline in hip BMD and spine BMD will be summarized for on-treatment data (ie, data collected up to 30 days after permanent discontinuation of study drug or all available data for subjects who were still on study drug) using observed data by treatment group and visit using descriptive statistics for subjects in the Hip and Spine DXA Analysis Sets, respectively, and compared between the 2 treatment groups at each visit using ANOVA, which includes baseline F/TDF for PrEP and treatment as fixed effects.

As a sensitivity analysis, hip BMD and spine BMD based on on-treatment data using the LOCF and BlOCF methods will be summarized using the Hip and Spine DXA Analysis Sets.

Median (Q1, Q3) and mean (95% CI) of the percentage change from baseline in hip BMD and spine BMD over time using observed data will be plotted by treatment group. Listings of hip and spine DXA results will be provided.

7.3.1.1. Subgroup Analysis for Percentage Change from Baseline in Hip and Spine Bone Mineral Density

The percentage change from baseline in hip and spine BMD will be summarized for on-treatment data using observed data by treatment group and visit within each subgroup specified in Section 3.4.2 [by baseline F/TDF for PrEP medications]. Baseline and percentage change from baseline will be compared by visit between the 2 treatment groups using ANOVA, which includes baseline F/TDF for PrEP and treatment as fixed effects for the age subgroups or only treatment as a fixed effect for the baseline F/TDF for PrEP subgroups.

7.3.2. Hip and Spine BMD Clinical Status

Analysis of hip and spine BMD clinical status will be based on the observed BMD values (ie, missing will be excluded).

For each subject and each visit, the BMD clinical status will be defined for hip BMD and spine BMD as follows based on the t-score from a male reference population:

Table 7-1. Normal, Osteopenia, and Osteoporosis as Defined by T-score

Clinical Status	BMD T-score
Normal	T-score ≥ -1.0
Osteopenia	-2.5 ≤ T-score < -1.0
Osteoporosis	T-score < -2.5

The number and percentage of subjects in each BMD clinical status (normal, osteopenia, and osteoporosis) will be summarized by visit and by baseline clinical status for both hip and spine. The distribution of the BMD clinical status will be compared between the 2 treatment groups adjusting for baseline clinical status and baseline F/TDF for PrEP using rank analysis of covariance {LaVange 2008}.

7.3.3. Gradation of the Percentage Change in Hip, Femur Neck, and Spine BMD

For each subject and each visit, percentage change from baseline in spine BMD will be classified into 6 categories: ≥ 5% decrease, ≥ 3% to < 5% decrease, > 0% to < 3% decrease, ≥ 0% to < 3% increase, ≥ 3% to < 5% increase, and ≥ 5% increase. Similarly, the percentage change from baseline in hip BMD and femur neck BMD will be classified into 6 categories: ≥ 7% decrease, ≥ 3% to < 7% decrease, > 0% to < 3% decrease, ≥ 0% to < 3% increase, ≥ 3% to < 7% increase, and ≥ 7% increase. The number and percentage of subjects in each category will be summarized by visit. The difference in the distribution of these categories between the treatment groups will be compared using a CMH test (row mean scores differ statistic) adjusting for baseline F/TDF for PrEP.

In addition, the number and percentage of subjects with percentage change from baseline in each cumulative categories (ie, ≥ 5% decrease, ≥ 3% decrease, no decrease [≥ 0% increase], ≥ 3% increase, and ≥ 5% increase for spine BMD; ≥ 7% decrease, ≥ 3% decrease, no decrease [≥ 0% increase], ≥ 3% increase, and ≥ 7% increase for hip and femur neck BMD) will be compared between treatment groups using a CMH test (general association statistic) adjusting for baseline F/TDF for PrEP based on the dichotomized response (ie, ≥ 5% decrease vs. < 5% decrease).

7.4. Renal-Related Safety Evaluations

Renal-related laboratory data will be summarized for the subjects in the Safety Analysis Set including on-treatment data collected up to 30 days after permanent discontinuation of study drug and all available data for subjects who were still on study drug or on a study drug interruption.

7.4.1. Beta-2-Microglobulin to Creatinine Ratio, Urine Retinol Binding Protein to Creatinine Ratio, Urine Creatinine

Percentage change from baseline in renal biomarkers of beta 2-microglobulin to creatinine ratio and urine RBP to creatinine ratio at Week 48 using observed on-treatment data are 2 of the 6 key (α-controlled) secondary endpoints.

Baseline, postbaseline, change from baseline, and percentage change from baseline in beta-2 microglobulin to creatinine ratio and urine RBP to creatinine ratio will be summarized for on-treatment data (ie, data collected up to 30 days after permanent discontinuation of study drug or all available data for subjects who were still on study drug) using observed data by treatment group and visit using descriptive statistics. Baseline and percentage change from baseline will be compared between the 2 treatment groups using a Van Elteren test stratified by baseline F/TDF for PrEP at each visit.

Baseline, postbaseline, and change from baseline in urine creatinine will be summarized by treatment group and visit using descriptive statistics. Baseline and change from baseline will be compared between the 2 treatment groups using a Van Elteren test stratified by baseline F/TDF for PrEP at each visit.

As a sensitivity analysis, renal biomarkers of beta 2-microglobulin to creatinine ratio and urine RBP to creatinine ratio based on on-treatment data using the LOCF and BlOCF methods will be summarized.

Median (Q1, Q3) percentage change from baseline in beta-2 microglobulin to creatinine ratio and urine RBP to creatinine ratio over time using observed data will be plotted by treatment group.

7.4.1.1. Subgroup Analysis for Beta-2-Microglobulin to Creatinine Ratio and Urine Retinol Binding Protein to Creatinine Ratio

The analysis of baseline, postbaseline, change from baseline, and percentage change from baseline in beta-2 microglobulin to creatinine ratio and urine RBP to creatinine ratio will be summarized by treatment group and visit within each baseline F/TDF for PrEP medications subgroup specified in Section 3.4.2. Baseline and percentage change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test at each visit.

7.4.2. Proteinuria by Quantitative Assessment

The distribution of the UP and UPCR categories at Week 48 using observed on-treatment data is 1 of the 6 key (α-controlled) secondary endpoints.

Subjects will be classified into three categories based on their urine protein (UP) and urine protein to creatinine ratio (UPCR) results: UPCR ≤ 200 mg/g (including subjects with UP < 4.0 mg/dL), UPCR > 200 mg/g, and Missing, where UPCR will only be calculated when UP ≥ 4.0 mg/dL. The number and percentage of subjects in each UP and UPCR category will be summarized for on-treatment data at Weeks 48 and 96 using observed data by baseline category

{KDIGO Guideline Development Staff 2013}. The distribution of the UP and UPCR categories will be compared by visit between the 2 treatment groups adjusting for baseline categories and baseline F/TDF for PrEP using rank analysis of covariance{LaVange 2008} (Appendix 2).

As a sensitivity analysis, UP and UPCR categories by visit based on on-treatment data using the LOCF and BlOCF methods will be summarized.

7.4.2.1. Subgroup Analysis for Proteinuria by Quantitative Assessment

The distribution of the UP and UPCR categories will be summarized for on-treatment data using observed data by treatment group at Week 48 and 96 within each baseline F/TDF for PrEP medications subgroup specified in Section 3.4.2. The distribution of the UP and UPCR categories will be compared by visit between the 2 treatment groups adjusting for baseline categories using rank analysis of covariance.

7.4.3. Proteinuria by Urinalysis (Dipstick)

The distribution of treatment-emergent proteinuria toxicity grade at the highest postbaseline graded value will be compared between treatment groups adjusting for baseline proteinuria toxicity grade and baseline F/TDF for PrEP using rank analysis of covariance {LaVange 2008}.

7.4.3.1. Subgroup Analysis for Proteinuria by Urinalysis (Dipstick)

The distribution of treatment-emergent proteinuria toxicity grade at the highest postbaseline graded value will be compared between treatment groups within each subgroup specified in Section 3.4.2. Comparisons between treatment groups will be adjusted for baseline F/TDF for PrEP (except for subgroups by baseline F/TDF for PrEP) and baseline proteinuria toxicity grade using rank analysis of covariance {LaVange 2008} at each visit.

7.4.4. Serum Creatinine

Change from baseline in serum creatinine at Week 48 using observed on-treatment is 1 of the 6 key (α-controlled) secondary endpoints.

Baseline, postbaseline, and change from baseline in serum creatinine will be summarized for on-treatment data using observed data by treatment group and visit using descriptive statistics. Baseline serum creatinine will be compared between the 2 treatment groups using ANOVA, which includes baseline F/TDF for PrEP and treatment as fixed effects. Change from baseline will be compared between the 2 treatment groups using an analysis of covariance model (ANCOVA) that includes baseline F/TDF for PrEP and treatment as fixed effects and baseline serum creatinine as a covariate.

As a sensitivity analysis, serum creatinine based on on-treatment data using the LOCF and BlOCF methods will be summarized.

Median (Q1, Q3) and mean (95% CI) of change from baseline in serum creatinine over time using observed data will be plotted by treatment group.

7.4.5. $eGFR_{CG}$

Baseline, postbaseline, and change from baseline in $eGFR_{CG}$ will be summarized by treatment group and visit using descriptive statistics. Baseline and change from baseline will be compared between the 2 treatment groups using a Van Elteren test stratified by baseline F/TDF for PrEP at each visit.

Median (Q1, Q3) of change from baseline in $eGFR_{CG}$ over time will be plotted by treatment group.

7.4.5.1. Subgroup Analysis for $eGFR_{CG}$

The analysis of baseline, postbaseline, and change from baseline in $eGFR_{CG}$ will be summarized by treatment group and visit using descriptive statistics within each subgroup specified in Section 3.4.2. Baseline and change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test for the subgroup of baseline F/TDF for PrEP and a Van Elteren test stratified by baseline F/TDF for PrEP for all other subgroups at each visit.

7.4.6. Proximal Renal Tubulopathy

Treatment-emergent proximal renal tubulopathy (PRT) events will be summarized by treatment group using the Safety Analysis Set by the following PTs (Appendix 10):

- Fanconi syndrome
- Fanconi syndrome acquired
- Renal tubular disorder
- Renal tubular dysfunction
- Renal tubular injury

The number and percentage of subjects who experienced PRT events will be summarized by treatment group and PT and compared between the 2 treatment groups using Fisher's exact test.

7.5. Body Weight, Height, BMI and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, BMI and vital signs as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline to each postbaseline analysis window

A baseline value will be defined as the last nonmissing value obtained on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

For body weight and BMI, baseline values will be compared between the 2 treatment groups using ANOVA, which includes baseline F/TDF for PrEP and treatment as fixed effects while change from baseline and percentage change from baseline (for body weight only) will be compared by visit between the 2 treatment groups using ANCOVA, which includes baseline F/TDF for PrEP and treatment as fixed effects and baseline value as a covariate.

For vital signs, no formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. In the same listing, a by-subject listing of body weight, height, and BMI will be provided.

7.6. Prior and Concomitant Medications

7.6.1. Nonstudy Drug Antiretroviral Medications

Any nonstudy drug antiretroviral (ARV) medications used prior to, during, or after the study (if collected) will be coded using the current version of the Gilead-modified World Health Organization (WHO) Drug Dictionary for ARV medications. The WHO preferred name and drug code will be attached to the clinical database. All nonstudy drug ARV medications will be listed. No inferential statistics will be provided.

7.6.2. Prior F/TDF for PrEP Medications

Prior F/TDF for PrEP medications are defined as any treatment course that includes branded F/TDF or generic F/TDF without any other 3rd ARV agents received prior to or on the first dose date of study drug.

The number and percentage of subjects with any prior F/TDF for PrEP (branded or generic F/TDF) will be summarized by treatment group and overall with other baseline HIV risk characteristics in Section 5.3.

For prior F/TDF for PrEP, medications with a start date prior to the first dosing date of study drug will be included regardless of the stop date. If a partial start date is entered, the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary.

7.6.3. Baseline F/TDF for PrEP Medications

Baseline F/TDF for PrEP medications (ie, recent relative to Study Day 1) are defined as any treatment course that includes branded F/TDF or generic F/TDF without any other 3rd ARV agents with an end date between Screening and first dose date (inclusive) of study drug.

The number and percentage of subjects with baseline F/TDF for PrEP (branded or generic F/TDF) will be summarized by treatment group and overall with other baseline HIV risk characteristics in Section 5.3.

For baseline F/TDF for PrEP, medications with a partial end date entered will be considered as a baseline medication if the month and year (if day is missing) of the end date is either between or the same as either the screening date or first dose date. Medications with a completely missing or year only end date will not be considered as a baseline medication.

7.6.4. PEP Medications While At Risk of HIV Infection During the Study

Post-exposure prophylaxis (PEP) is defined as treatment with any non-study drug ARV agent other than F/TDF (or generic F/TDF), cabotegravir or HIV vaccine while subjects are at risk of HIV infection as defined in Section 6.2.3.

The number of subjects with any PEP use and the number of PEP uses per subject while at risk of HIV infection during the DB phase, while on-treatment and while off-treatment and at risk of HIV infection will be summarized for the FAS.

The number of PEP uses per subject will be based on unique PEP medication start dates within each subject. Multiple ARV medications with overlapping start and end dates will be counted as only one PEP use. Consecutive PEP medications where the complete medication end date of one PEP medication differs from the complete medication start date of another PEP medication by one day or less will be counted as only one PEP use.

For PEP uses while at risk of HIV infection during the DB phase, if the start or stop date of the ARV medication is incomplete, the month and year (or year alone, if month is not recorded) of the start or stop date will be used to determine whether the ARVs occurred during the at risk of HIV infection period or not. The medication occurred during the at risk of HIV infection period if the month and year of the start or stop (or year of the start or stop, if month is not recorded) of the medication does not meet either of the following criteria:

- The month and year of start of the medication is after the date of the end of the at risk of HIV infection period
- The month and year of stop of the medication is on or before the date of the first dose of study drug

If the start and stop date of ARV medications are complete, the start date is not after the date of the end of the at risk of HIV infection period and the stop date is not on or before first dose date, or the ARV medications are marked as ongoing and start date is on or before the date of the end of the at risk of HIV infection period, the non-ARV medications are considered as occurring during the at risk of HIV infection period. Medications with completely missing start and end dates will not be considered as occurring while at risk of HIV infection during the study.

PEP uses while on-treatment at risk of HIV infection are defined similar to the above PEP uses while at risk of HIV infection, but replacing the date of the end of the at risk of HIV infection period with the minimum of the last dose date and end of the at risk of HIV infection period for subjects that have permanently discontinued study drug. For subjects that have not permanently discontinued study drug, PEP uses are defined as above for PEP uses while at risk of HIV infection.

For PEP uses while off study drug for PrEP (off-treatment) at risk of HIV infection are defined similar to the above PEP uses while at risk of HIV infection, but replacing the first dose date with the last dose date for subjects that have permanently discontinued study drug. Subjects that have not permanently discontinued study drug or subjects that permanently discontinued study drug, but whose end of at risk of HIV infection period is on or before the last dose date will be excluded.

The denominator for subjects with any PEP use or on-treatment PEP use while at risk of HIV infection during the study will be the FAS. The denominator for subjects with off-treatment PEP use while at risk of HIV infection during the study will be subjects in the FAS who have permanently discontinued study drug and have at least one post-last dose HIV laboratory assessment (from either local or Covance laboratory).

7.6.5. Concomitant Non-ARV Medications

Concomitant non-ARV medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of concomitant medications from Study Day 1 up to the date of the DB phase last dose of study drug will be summarized (number and percentage of subjects) by treatment group and preferred name. Multiple drug use (by preferred name) will be counted only once per subject. The summary will be sorted by decreasing total frequency. For drugs with the same frequency, sorting will be done alphabetically.

If the start or stop date of non-ARV medications is incomplete, the month and year (or year alone, if month is not recorded) of the start or stop date will be used to determine whether the non-ARVs are concomitant or not. The medication is concomitant if the month and year of the start or stop (or year of the start or stop, if month is not recorded) of the medication does not meet either of the following criteria:

- The month and year of start of the medication is after the date of the DB phase last dose of study drug
- The month and year of stop of the medication is before the date of the first dose of study drug

If the start and stop date of non-ARV medications are complete, the start date is not after the DB phase last dose date and the stop date is not before first dose date, or the non-ARV medications are marked as ongoing and start date is on or before the DB phase last dose date, the non-ARV medications are concomitant for the DB phase of the study. Medications with completely missing start and stop dates will be included in the concomitant medication non-ARV summary, unless otherwise specified.

Summaries of non-ARV concomitant medications will be provided for the Safety Analysis Set. Subjects with any non-ARV concomitant medications will be listed. No inferential statistics will be provided.

7.7. Other Safety Measures

Physical examination data was not collected in the eCRF. Therefore, it will not be included in the analysis.

7.8. Changes From Protocol-Specified Safety Analyses

The criterion for a nonmissing postbaseline BMD value is not required for either the Hip or Spine DXA Analysis Sets. As the BMD sensitivity analyses using the BlOCF imputation method do not require subjects to have at least 1 postbaseline value this condition is removed from the Hip and Spine DXA Analysis Sets used for all BMD analyses.

8. PHARMACOKINETIC ANALYSES

The PK analysis was already performed in the primary analysis and will not be repeated in this analysis.

9. SEXUAL RISK BEHAVIOR

Sexual risk characteristics including outcomes of high-risk sexual behavior (sexually transmitted infections [STI]) while at risk of HIV infection during the DB phase of the study will be summarized for the subjects in the FAS.

All sexual risk characteristics data will be included in data listings.

9.1. Sexually Transmitted Infections While At Risk of HIV Infection During the DB phase

STIs considered to have occurred while at risk of HIV infection are defined as those occurring after the first dose date (excluding the Day 1 first dose date) and on or before the end date (end date Day 1 date +1) where end date is defined as the last at risk of HIV infection date during the DB phase defined in Section 6.2.3.

9.2. Sexually Transmitted Infections

9.2.1. Definition of STI Infections from Laboratory Data While At Risk of HIV Infection During the DB phase

9.2.1.1. Definition of Chlamydia or Gonorrhea Infection by Anatomic Location (Rectal, Pharyngeal, or Urethral) from Laboratory Data

Subjects with chlamydia or gonorrhea infection at each anatomic location are defined as subjects with results of either 'detected' from the urine Covance central laboratory tests or 'positive' from the rectal or pharyngeal local laboratory tests captured on the Local Lab eCRFs for chlamydia or gonorrhea.

For each STI (chlamydia or gonorrhea) and anatomic location (rectal, pharyngeal, or urethral) separately, the number of unique infection events is defined based on unique laboratory collection dates within each subject; however, within a subject, multiple positive infection results from laboratory collection dates within a 14 day period will be counted as only one infection event on the date of the first positive result.

9.2.1.2. Definition of Syphilis Infection (Investigator Reported)

Subjects with syphilis infection are defined as subjects with a diagnosis of either new, re-infection or missing syphilis infection status (excluding treatment failures) from the Syphilis Diagnosis eCRF.

The number of unique syphilis infection events is defined based on unique diagnosis dates within each subject for each disease stage and disease status as captured on the Syphilis Diagnosis eCRF with a syphilis infection status of new, re-infection or missing (excluding treatment failures).

9.2.2. Summaries of Gonorrhea, Chlamydia or Syphilis STIs While At Risk of HIV Infection During the DB phase

The following summaries of STIs while at risk of HIV infection will be provided by treatment group for the FAS:

- Gonorrhea or Chlamydia (based on laboratory data)

  Rectal

  Pharyngeal

  Urethral (Urine)

- Gonorrhea (based on laboratory data)

  Rectal

  Pharyngeal

  Urethral (Urine)

- Chlamydia (based on laboratory data)

  Rectal

  Pharyngeal

  Urethral (Urine)

- Syphilis (based on investigator report)

  Disease stage (Primary, Early Latent, Secondary, Tertiary, Late Latent, Other or Missing)

  Status (New, Re-infection or Missing)

For each STI summary above, the number and percentage of subjects will be summarized by treatment group and overall on the FAS.

For each STI summary above, the STI incidence rate per 100 person-years of follow-up will be computed as the number of unique events occurring while at risk of HIV infection divided by the summation of all subjects' total number of years (where a year is 365.25 days) of follow-up while at risk of HIV infection (defined in Section 9.1.) The STI incidence rates will be summarized by treatment group and overall for the FAS.

9.2.3. Incidence of Gonorrhea or Chlamydia STIs Based on Laboratory Data by Visit While At Risk of HIV Infection During the DB phase

The incidence of new STIs based on laboratory data will be summarized by visit and treatment group for the FAS for subjects with

- Any Gonorrhea or Chlamydia (rectal, pharyngeal, or urethral)
- Rectal Gonorrhea or Rectal Chlamydia

Incidence of these STIs by visit will be plotted by treatment group based on the FAS.

9.3. Anal Intercourse Partners While At Risk of HIV Infection During the DB phase (CASI Questionnaire)

The number of anal intercourse partners from CASI questionnaire responses will be summarized by treatment group and visit while at risk of HIV infection during the study, using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) as well as the number and percentage of subjects with 0, 1, 2, 3, 4-5, 6-10 and ≥ 11 partners on the FAS. The following summaries of number of anal intercourse partners will be provided:

- Unprotected Receptive Anal Intercourse (URAI) Partners
- Unprotected Insertive Anal Intercourse (UIAI) Partners
- Anal Intercourse Partners

While at risk of HIV infection during the study includes visits occurring through the upper limit of the analysis window corresponding to the last at-risk of HIV infection date as defined in Section 6.2.3.

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11. SOFTWARE

SAS® Version 9.4 (SAS Institute Inc., Cary, NC.) is to be used for all programming of tables, listings, and figures.

nQuery Advisor® Version 7.0 (Statistical Solutions, Cork, Ireland.) is to be used for sample size and power calculation.

12. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

13. APPENDICES

Appendix 1. Study Procedures Table

Appendix Table 1. Study Procedures Table

			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[o]	X	X	X	X		X	X	X		X	X	X	X	X		X	X	X
Vital Signs[g]	X	X[o]	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[ac] (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)[ac]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample for Gonorrhea and Chlamydia	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rapid HIV 1 Ag/Ab Test (In Clinic)[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV 1 Ab/Ag[q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

			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]**
HIV 1 RNA by PCR[r]	X	X[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dipstick Urinalysis (In Clinic)	X																			
Urinalysis, Urine Protein, Urine Chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																				
Blood Sample for Chemistry Profile[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Hematology Profile[i]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for DBS[j]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood Sample for Syphilis testing[k] (Local Laboratory)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B Testing (HBsAg/HBsAb/HBcAb)	X				X		X		X		X	X[ad]	X[ad]		X		X	X[ad]		
Hepatitis C Testing (HCV Ab)	X						X				X	X[ae]	X[ae]				X	X[ae]		
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)[l]			X																	
Anytime PK blood sample (plasma only)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
CCI																				
CASI Questionnaire[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Randomization in IXRS		X																		

			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]**
Risk Reduction/ Adherence Counseling	X[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
DXA Scan (Hip and Spine)		X[v]					X[w]				X[w]		X[w]				X[w]			X[x]
Study Drug Dispensation and Accountability		X[y]	X	X	X	X	X	X	X	X	X	X	X[z]	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 subjects 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 subjects 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 subjects 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 subjects 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

a All study visits in the double blind phase are to be scheduled relative to the Day 1 visit date. Visit windows are ± 2 days of the protocol specified date through Week 12, ± 14 days of the protocol specified date through the End of Blinded Treatment Phase visit, unless otherwise specified.
b End of Blinded Treatment Phase visit to occur after all subjects reach Week 96.
c Study visits are to be completed within ± 14 days of the protocol specified visit date based on the End of Blinded Treatment Phase visit.
d Subjects will continue study visits every 12 weeks until study drug F/TAF is commercially available in their region (except Denmark and the United Kingdom).
e Must be completed 30 days after discontinuing study drug. **All subjects who have received at least one dose of study drug will be required to complete a follow-up visit**. For the purpose of scheduling a 30 Day Follow Up visit, a ± 14 days window may be used.
f Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Phase visit.
g Vital signs measurement including blood pressure, pulse, respiration rate, and temperature. After the Day 1 visit, vital signs completed when clinically indicated.
h Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN).

i Complete blood count (CBC) with differential and platelet count.
j Blood sample collected for DBS testing to be stored at central laboratory.
k Local STI testing for syphilis.
l Trough PK blood samples to evaluate the pharmacokinetics of intracellular TFV DP and FTC TP, plasma TFV and FTC. The blood sample should be taken approximately 24 hours after the last dose of study drug and prior to administration of study drug the day of the visit.
[redacted]
n Computer assisted self interview (CASI).
o If Day 1 is completed > 7 days after the screening visit.
p 4th generation rapid HIV 1 Ab/Ag or 3rd generation rapid HIV 1 Ab test may be used. If 4th generation rapid HIV 1 Ag/Ab or 3rd generation rapid HIV 1 Ab test is positive, a retest will be completed. At Screening or Day 1, if rapid retest is positive the subject is a screen failure. At all other visits if rapid retest is positive, then HIV 1 RNA by PCR test and sample collection for possible genotypic testing will be completed.
q At Screening, if HIV 1 Ab/Ag is positive the subject is a screen failure. At all other visits if HIV 1 Ab/Ag is positive, then HIV 1 RNA by PCR test and sample collection for possible genotypic testing will be completed.
r At Screening or Day 1, if the subject has a negative rapid test, but has signs or symptoms of acute HIV 1 infection, an HIV 1 RNA by PCR test will be completed and if HIV 1 RNA by PCR is positive, subject cannot participate in the study. At all other visits, HIV 1 RNA by PCR and sample collection for possible genotypic resistance testing will be completed for any subjects who (1) have a positive retest rapid HIV 1 Ab/Ag test or (2) have a positive HIV 1 Ab/Ag test or (3) show symptoms consistent with acute infection regardless of the results of the rapid tests, (4) have a recent exposure that is considered high risk for HIV infection, or (5) have been confirmed HIV infected. If HIV infection is confirmed, subject will discontinue study drug immediately and should return for an ESDD visit within 72 hours. The subject will receive counseling and be referred for appropriate care. If viral load > 400 copies/mL the collected sample will be sent for genotypic resistance testing.
s At Day 1, HIV 1 RNA by PCR and sample collection for possible genotypic testing will be completed for any subjects who show symptoms consistent with acute HIV 1 infection regardless of the results of the rapid tests.
t Every 24 Weeks only.
u Only risk reduction counseling at Screening.
v DXA scans of hip and spine in substudy participants (within 14 days prior to or after the start of treatment).
w DXA scans are to be scheduled ± 6 weeks to the protocol specified dates for the Week 48, Week 96, End of Blinded Treatment Phase, and OL Week 48 visits.
x DXA scan of hip and spine in substudy participants (if discontinuation is > 12 weeks from the prior DXA scan).
y Only study drug dispensation at Day 1.
z OL drug dispensation (all eligible subjects will receive F/TAF).
aa Study drug dispensing: No study drug dispensation at OL WK 48 except for subjects continuing on past OL WK 48 due to commercial drug unavailability.
ab No study drug dispensed.
ac Swabs may be self administered by the subject at the discretion of the investigator.
ad Hepatitis B testing (HBsAg, HBsAb, HBcAb) to be completed every 24 weeks. Hepatitis B testing to be completed at the End of Blinded Treatment Phase visit if > than 24 weeks from prior testing.
ae Hepatitis C testing (HCV Ab) to be completed every 48 weeks. Hepatitis C testing to be completed at the End of Blinded Treatment Phase visit if > 48 weeks from prior testing.

Appendix 2. TFL Mocks

Appendix Table 2. HIV Infection Rates While At Risk of HIV Infection (Rate Ratio Method), Full Analysis Set

	F/TAF (N=xxx)	F/TDF (N=xxx)	F/TAF vs. F/TDF	
			p-value	Rate Ratio (95.003% CI)
Person-years of Follow-Up	xxxx.x	xxxx.x		
Number of HIV Infection Events	xx	xx		
HIV Infection Rate per 100 Person-years	x.xxx	x.xxx	0.xxxx	x.xxx (x.xxx, x.xxx)
95% Exact CI	(x.xxx, x.xxx)	(x.xxx, x.xxx)		

HIV infection based on serologic evidence (excluding HIV vaccinated subjects), virologic evidence and/or evidence of acute infection.
Person years is the summation of all subjects' total number of years (year 365.25 days) of follow up in study between the first dose date and either 1) date of HIV diagnosis for subjects with HIV or 2) date of last post baseline HIV laboratory test (incl. 30 day follow up and either local or Covance lab) for subjects not infected with HIV.
P value for the superiority test comparing the HIV infection rate ratio estimation of F/TAF / F/TDF was from a Poisson model.
95.003% CI of HIV infection rate ratio is from a generalized model with a Poisson distribution and logarithmic link with treatment as a main effect.
95% exact CI was based on the single Poisson rate parameter method (Ulm 1990).

Appendix Table 3. HIV Infection Rate by Subgroup While At Risk of HIV Infection, Full Analysis Set

Subgroup		F/TAF (N=xxx)	F/TDF (N=xxx)
Overall	N Person-years of Follow-Up Number of HIV Infection Events HIV Infection Rate per 100 Person-years 95% Exact CI	xx xx.x xx x.xxx (x.xxx, x.xxx)	xx xx.x xx x.xxx (x.xxx, x.xxx)
Age			
< 25	N Person-years of Follow-Up Number of HIV Infection Events HIV Infection Rate per 100 Person-years 95% Exact CI	xx xx.x xx x.xxx (x.xxx, x.xxx)	xx xx.x xx x.xxx (x.xxx, x.xxx)
≥ 25	N Person-years of Follow-Up Number of HIV Infection Events HIV Infection Rate per 100 Person-years 95% Exact CI	xx xx.x xx x.xxx (x.xxx, x.xxx)	xx xx.x xx x.xxx (x.xxx, x.xxx)
Etc.			

95% exact CI was based on the single Poisson rate parameter method (Ulm 1990).

Appendix Table 4. Summary of Statistical Testing for Key Safety Endpoints Using Fallback Procedure, Safety Analysis Set

Testing (F/TAF vs F/TDF)	Reported P-value	Pre-specified Alpha	Adjusted Alpha
Percentage Change from Baseline in Hip BMD at Week 48	0.xxx	0.xx	0.xx
Percentage Change from Baseline in Spine BMD at Week 48	0.xxx	0.xx	0.xx
Percentage Change from Baseline in Urine Beta-2-microglobulin to Creatinine Ratio at Week 48	0.xxx	0.xx	0.xx
Percentage Change from Baseline in Urine RBP to Creatinine Ratio at Week 48	0.xxx	0.xx	0.xx
Distribution of UP and UPCR categories at Week 48	0.xxx	0.xx	0.xx
Change from Baseline in Serum Creatinine at Week 48	0.xxx	0.xx	0.xx

There are 6 key safety endpoints for the study. Each endpoint will be tested individually. Multiplicity adjustment is performed with a fallback procedure in the sequential order shown with pre specified 2 sided alpha levels.
Reported P values from Tables xx, xx, xx, xx, xx, and xx, respectively.
Observed on treatment data collected up to 30 days after last dose of study drug or all postbaseline data for subjects still on study drug.

Appendix Table 5. HIV Infection Rates (Comparison to Predicted HIV Incidence Rate from Rectal Gonorrhea Rates), Full Analysis Sets

	Observed Rectal Gonorrhea Incidence Rate per 100 PY	Expected HIV Incidence Rate per 100 PY (95% Prediction Interval) Based on Observed Rectal Gonorrhea Rate	Observed F/TAF or F/TDF HIV Infection Rate per 100 PY (95% Exact CI)
F/TAF			
FAS, While At Risk of HIV Infection	x.xxx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
Per Protocol, On-Treatment	x.xxx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
F/TDF			
FAS, While At Risk of HIV Infection	x.xxx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
Per Protocol, On-Treatment	x.xxx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)

Observed HIV infection rate and rectal gonorrhea incidence rate (number of events per 100 person years [PY], includes multiple events per subject, based on local laboratory tests) from GS US 412 2055. 95% exact CI from the single Poisson rate parameter (Ulm 1990).
Expected HIV incidence rate based on a regression model of rectal gonorrhea and HIV incidence rates in the absence of HIV prophylaxis (Mullick 2019).
Programming note: The HIV infection incidence rates will be computed on the populations and follow up timeframes specified in the primary efficacy analyses (Section 6.1.1 6.2.3) as well as the PP on treatment sensitivity analysis (Section 6.2.6.) The rectal gonorrhea incidence rates will be computed based on laboratory data as specified in Section 9.2.1.1.

Appendix Table 6. Shift Table of Urine Protein to Creatinine Ratio Category (≤ 200 vs. > 200 mg/g) by Baseline Category, Safety Analysis Set

	F/TAF			F/TDF			F/TAF vs. F/TDF
	Baseline			Baseline			
	≤ 200 mg/g (N =xx)	> 200 mg/g (N =xx)	Missing (N =xx)	≤ 200 mg/g (N =xx)	> 200 mg/g (N =xx)	Missing (N =xx)	p-value
Week 48							
≤ 200 mg/g	xx (x.x%)	xx (x.x%)	xx	xx (x.x%)	xx (x.x%)	xx	0.xx
> 200 mg/g	xx (x.x%)	xx (x.x%)	xx	xx (x.x%)	xx (x.x%)	xx	
Missing	xx	xx	xx	xx	xx	xx	
Week 96							
≤ 200 mg/g	xx (x.x%)	xx (x.x%)	xx	xx (x.x%)	xx (x.x%)	xx	0.xx
> 200 mg/g	xx (x.x%)	xx (x.x%)	xx	xx (x.x%)	xx (x.x%)	xx	
Missing	xx	xx	xx	xx	xx	xx	

Denominator for percentage was the number of subjects with nonmissing values at both baseline and each postbaseline visit for each baseline category.
Urine protein to creatinine ratio (UPCR) were only calculated when corresponding urine protein (UP) > 4.0 mg/dL.
UPCR "< 200 mg/g" category includes both subjects with UP < 4.0 mg/dL and subjects with UPCR < 200 mg/g.
P values for treatment comparison were from the rank analysis of covariance adjusting for baseline category and baseline F/TDF for PrEP.

Appendix 3. Region Definition

Region	Country Name	State	No. of Subjects in Safety Analysis Set (N=5387)	Total No. of Subjects by Region in Safety Analysis Set (N=5387)
Region 1 (Canada)	CANADA (CAN)		353	353
Region 2 (European Union)	AUSTRIA (AUT)		77	1814
	DENMARK (DNK)		202	
	FRANCE (FRA)		32	
	GERMANY (DEU)		370	
	IRELAND (IRL)		78	
	ITALY (ITA)		58	
	NETHERLANDS (NLD)		71	
	SPAIN (ESP)		414	
	UNITED KINGDOM (GBR)		512	
Region 3 (US-Northeast)	UNITED STATES (USA)	CT	40	142
	UNITED STATES (USA)	MA	38	
	UNITED STATES (USA)	NJ	19	
	UNITED STATES (USA)	NY	32	
	UNITED STATES (USA)	PA	13	
Region 4 (US-Midwest)	UNITED STATES (USA)	IL	52	200
	UNITED STATES (USA)	MI	120	
	UNITED STATES (USA)	OH	2	
	UNITED STATES (USA)	WI	6	
	UNITED STATES (USA)	MN	20	

Region	Country Name	State	No. of Subjects in Safety Analysis Set (N=5387)	Total No. of Subjects by Region in Safety Analysis Set (N=5387)
Region 5 (US-South)	UNITED STATES (USA)	DC	106	1255
	UNITED STATES (USA)	FL	543	
	UNITED STATES (USA)	GA	74	
	UNITED STATES (USA)	LA	17	
	UNITED STATES (USA)	NC	81	
	UNITED STATES (USA)	TX	434	
Region 6 (US-West)	UNITED STATES (USA)	CA	1228	1623
	UNITED STATES (USA)	CO	123	
	UNITED STATES (USA)	NV	63	
	UNITED STATES (USA)	WA	141	
	UNITED STATES (USA)	NM	68	

US regions of residence are defined by the {Centers for Disease Control (CDC) 2016}and U.S. Census Bureau as follows (**bolded** states represent GS US 412 2055 sites):
Northeast: **Connecticut**, Maine, **Massachusetts**, New Hampshire, **New Jersey**, **New York**, **Pennsylvania**, Rhode Island, and Vermont
Midwest: **Illinois**, Indiana, Iowa, Kansas, **Michigan**, **Minnesota**, Missouri, Nebraska, North Dakota, **Ohio**, South Dakota, and **Wisconsin**
South: Alabama, Arkansas, Delaware, **District of Columbia**, **Florida**, **Georgia**, Kentucky, **Louisiana**, Maryland, Mississippi, **North Carolina**, Oklahoma, South Carolina, Tennessee, **Texas**, Virginia, and West Virginia
West: Alaska, Arizona, **California, Colorado**, Hawaii, Idaho, Montana, **Nevada**, **New Mexico**, Oregon, Utah, **Washington**, and Wyoming
U.S. dependent areas: American Samoa, Guam, the Northern Mariana Islands, Puerto Rico, the Republic of Palau, and the U.S. Virgin Islands

Appendix 4. Selected Medical History

Number and percentage of subjects with selected medical history of Diabetes Mellitus, Hypertension, Cardiovascular Disease, and Hyperlipidemia will be summarized by treatment as baseline disease characteristics. A subject who had medical history of one of these diseases is a subject who experience at least one of the following events:

- At least 1 medical history record with MedDRA PT (mh.MDRPT) in the following selected PT listing for the corresponding disease with start date on or prior to the DB phase first dose date.

- At least 1 AE record with MedDRA PT (ae.MDRPT) in the following selected PT listing for the corresponding disease with start date on or prior to the DB phase first dose date.

- At least 1 concomitant medications record with medication class and indication in the following selected listing for the corresponding disease with start date on or prior to the DB phase first dose date.

If the start date is incomplete but the month and year (or year alone) of the start date is the same as or before the month and year (or year alone) of the first dosing date of randomized study drug, the event will be included. If the start date is completely missing, the event will be included.

Four variables (ie, DIABETES, HTENSION, CARDDIS, and HLIPDEM) will be added to raw Medical History and Adverse Events datasets. A medical history or an AE record will be flagged for a disease of interest if its MedDRA PT included in the prespecified PT list for the corresponding disease of interest, which include all PTs from the narrow or broad search of the following SMQs under MedDRA 19.1 provided by Gilead DSPH and reviewed by Gilead medical monitors.

Disease of Interest	SMQ Source
Diabetes Mellitus (DIABETES)	Hyperglycaemia/new onset diabetes mellitus (SMQ) Narrow Scope Term
Hyperlipidemia (HLIPDEM)	Dyslipidaemia (SMQ)
Hypertension (HTENSION)	Hypertension (SMQ)
Cardiovascular disease (CARDDIS)	Ischaemic central nervous system vascular conditions (SMQ) Narrow Scope Term
	Myocardial infarction (SMQ) Narrow Scope Term
	Other ischaemic heart disease (SMQ) Narrow Scope Term

Similarly, two variables (ie, DRUGF and DRUGTYP) will be added to raw Concomitant Medication dataset. A concomitant medication record will be flagged for a disease of interest if its medication class and indication included in the following listing for the corresponding disease of interest.

The selected combination of medication class and indication are listed as follows, which was reviewed by Gilead medical monitors.

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
Hypertension (HTENSION)			
1	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM		LISINOPRIL
2	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ANTI HYPERTENSIVE	LOSARTAN
3	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPENTENSION	RAMIPRIL
4	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	CAPTOPRIL
5	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	ENALAPRIL
6	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	HYDROCHLOROTHIAZIDE W/OLMESARTAN
7	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	OLMESARTAN MEDOXOMIL
8	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	RAMIPRIL
9	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	SALUTEC
10	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	VALSARTAN
11	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION STAGE I	CAPTOPRIL
12	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION STAGE 1	CANDESARTAN
13	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	BENIGN ESSENTIAL HYPERTENSION	LISINOPRIL
14	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	BENIGN ESSENTIAL HYPERTENSION	LOSARTAN
15	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL (PRIMARY) HYPERTESION	ZESTORETIC
16	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	COROVAL B
17	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	ENALAPRIL MALEATE
18	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	LISINOPRIL
19	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	LOSARTAN
20	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	TRIBENZOR

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
21	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	ZESTORETIC
22	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL PRIMARY HYPERTENSION	IRBESARTAN
23	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	COVERAM
24	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	ENALAPRIL
25	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	IRBESARTAN
26	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	LISINOPRIL
27	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	LOSARTAN
28	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	LOSARTAN POTASSIUM
29	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	RAMIPRIL
30	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BOLD PRESSURE	LOSARTAN
31	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HISTORY OF MYOCARDITIS	RAMIPRIL
32	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HTN	ZESTORETIC
33	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERRTENSION	ZESTORETIC
34	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTEENSION	LISINOPRIL
35	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	AMLODIPINE W/HYDROCHLOROTHIAZIDE/ VALSARTAN
36	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	AMLODIPINE W/VALSARTAN
37	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	BENAZEPRIL
38	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	BENAZEPRIL HYDROCHLORIDE
39	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	BENICAR HCT
40	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	BI PREDONIUM

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
41	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	CANDESARTAN
42	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	CANDESARTAN CILEXETIL
43	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	CAPTOPRIL
44	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	CO DIOVAN
45	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	COROVAL B
46	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	DIOVAN AMLO
47	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	DIOVAN TRIPLE
48	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	EDARBYCLOR
49	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	ENALAPRIL
50	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	ENALAPRIL MALEATE
51	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	FOSINOPRIL
52	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	HYDROCHLOROTHIAZIDE W/LOSARTAN
53	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	HYZAAR
54	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	IRBESARTAN
55	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	KARVEA HCT
56	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	LISINOPRIL
57	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	LOSARTAN
58	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	LOSARTAN POTASSIUM
59	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	NAPRIX A
60	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	OLMESARTAN MEDOXOMIL
61	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	PERINDOPRIL ERBUMINE

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
62	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	PRITORPLUS
63	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	QUINAPRIL
64	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	RAMIPRIL
65	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	SALUTEC
66	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	TELMISARTAN
67	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	TRIBENZOR
68	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	VALSARTAN
69	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	VASERETIC
70	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	ZESTORETIC
71	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION ESSENTIAL	CANDESARTAN CILEXETIL
72	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION ESSENTIAL	DIOVAN TRIPLE
73	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION, BENIGN	LISINOPRIL
74	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION, BILATERAL LOWER LEG SWELLING	LISINOPRIL
75	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION, ESSENTIAL	ZESTORETIC
76	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION, WORSENING HYPERTENSION	LISINOPRIL
77	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSIONPROPHYLAXIS	RAMIPRIL
78	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSIVE	RAMIPRIL
79	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSIVE CRISIS	CAPTOPRIL
80	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENTION	LISINOPRIL
81	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTONIA	RAMIPRIL
82	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPOKALEMIA	LOSARTAN POTASSIUM

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
83	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	POOR CONTROL OF BLOOD PRESSURE	LISINOPRIL
84	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	PREVENTATIVE FOLLOWING ACUTE MYCARDIAL INFARCTION	PERINDOPRIL
85	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	PRIMARY ESSENTIAL HYPERTENSION	ENALAPRIL MALEATE
86	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	PROTEINURIA	BENAZEPRIL
87	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	PROTEINURIA	ENALAPRIL
88	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	PROTEINURIA	LISINOPRIL
89	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	WORSENING HYPERTENSION	BENAZEPRIL
90	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	WORSENING HYPERTENSION	PERINDOPRIL
91	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	WORSENING HYPERTENSION	PRETERAX ARGININE
92	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	WORSENING OF HYPERTENSION	LISINOPRIL
93	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	WORSENING OF HYPERTENSION	RAMIPRIL
94	ANTIHYPERTENSIVES	BENIGN HIGH BLOOD PRESSURE	DOXAZOSIN
95	ANTIHYPERTENSIVES	EXACERBATION OF HYPERTENSION	CLONIDINE
96	ANTIHYPERTENSIVES	HEADACHE	HYDRALAZINE
97	ANTIHYPERTENSIVES	HIGH BLOOD PRESSURE	CLONIDINE HYDROCHLORIDE
98	ANTIHYPERTENSIVES	HIGH BLOOD PRESSURE	RILMENIDINE
99	ANTIHYPERTENSIVES	HYPERTENSION	CLONIDINE
100	ANTIHYPERTENSIVES	HYPERTENSION	CLONIDINE HYDROCHLORIDE
101	ANTIHYPERTENSIVES	HYPERTENSION	DOXAZOSIN
102	ANTIHYPERTENSIVES	HYPERTENSION	DOXAZOSIN MESILATE
103	ANTIHYPERTENSIVES	HYPERTENSION	HYDRALAZINE
104	ANTIHYPERTENSIVES	HYPERTENSION	HYDRALAZINE HYDROCHLORIDE
105	ANTIHYPERTENSIVES	HYPERTENSION	METHYLDOPA
106	ANTIHYPERTENSIVES	HYPERTENSION	TADALAFIL
107	ANTIHYPERTENSIVES	PULMONARY HYPERTENSION	TADALAFIL

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
108	ANTIHYPERTENSIVES	VASODILATION STENT PROCEDURE	HYDRALAZINE
109	ANTIHYPERTENSIVES	WORSENING HYPERTENSION	HYDRALAZINE HYDROCHLORIDE
110	BETA BLOCKING AGENTS	ARTERIAL HYPERTENSION	ATENOLOL
111	BETA BLOCKING AGENTS	ARTERIAL HYPERTENSION	METOPROLOL SUCCINATE
112	BETA BLOCKING AGENTS	ARTERIAL HYPERTENSION / ICHEMIC HEART DISEASE	BISOPROLOL
113	BETA BLOCKING AGENTS	ESSENTIAL HYPERTENSION	METOPROLOL
114	BETA BLOCKING AGENTS	HEART FAILURE AND HYPERTENSION	CARVEDILOL
115	BETA BLOCKING AGENTS	HEART HEALTH	ATENOLOL
116	BETA BLOCKING AGENTS	HIGH BLOOD PRESSURE	ATENOLOL
117	BETA BLOCKING AGENTS	HIGH BLOOD PRESSURE	BISOPROLOL W/HYDROCHLOROTHIAZIDE
118	BETA BLOCKING AGENTS	HIGH BLOOD PRESSURE	METOPROLOL
119	BETA BLOCKING AGENTS	HISTORY OF MYOCARDITIS	BISOPROLOL
120	BETA BLOCKING AGENTS	HYPERTENSION	ATENOLOL
121	BETA BLOCKING AGENTS	HYPERTENSION	BISOPROLOL FUMARATE
122	BETA BLOCKING AGENTS	HYPERTENSION	CARVEDILOL
123	BETA BLOCKING AGENTS	HYPERTENSION	LABETALOL
124	BETA BLOCKING AGENTS	HYPERTENSION	METOPROLOL
125	BETA BLOCKING AGENTS	HYPERTENSION	METOPROLOL SUCCINATE
126	BETA BLOCKING AGENTS	HYPERTENSION	METOPROLOL TARTRATE
127	BETA BLOCKING AGENTS	HYPERTENSION	NEBICARD V
128	BETA BLOCKING AGENTS	HYPERTENSION	NEBICARD H
129	BETA BLOCKING AGENTS	HYPERTENSION	NEBIVOLOL
130	BETA BLOCKING AGENTS	HYPERTENSION	NEBIVOLOL HYDROCHLORIDE
131	BETA BLOCKING AGENTS	HYPERTENSION	PROPRANOLOL
132	BETA BLOCKING AGENTS	HYPERTENSION	PROPRANOLOL HYDROCHLORIDE
133	BETA BLOCKING AGENTS	HYPERTENSION AND MIGRAINE	ATENOLOL
134	BETA BLOCKING AGENTS	HYPERTENSION ESSENTIAL	ATENOLOL
135	BETA BLOCKING AGENTS	HYPERTENTION	METOPROLOL SUCCINATE
136	BETA BLOCKING AGENTS	HYPETENSION	BISOPROLOL

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
137	BETA BLOCKING AGENTS	PAROXYSM OF SINUS TACHYCARDIA	PROPRANOLOL
138	BETA BLOCKING AGENTS	PRIMARY ESSENTIAL HYPERTENSION	CARVEDILOL
139	BETA BLOCKING AGENTS	RAPID HEART BEAT	METOPROLOL SUCCINATE
140	CALCIUM CHANNEL BLOCKERS	ANTIHYPERTENSIVE	AMLODIPINE
141	CALCIUM CHANNEL BLOCKERS	ARTERIAL HYPERTENSION	AMLODIPINE
142	CALCIUM CHANNEL BLOCKERS	ARTERIAL HYPERTENSION	VERAPAMIL
143	CALCIUM CHANNEL BLOCKERS	ATRIAL FIBRILLATION	DILTIAZEM
144	CALCIUM CHANNEL BLOCKERS	ELEVATED BLOOD PRESSURE	AMLODIPINE
145	CALCIUM CHANNEL BLOCKERS	ELEVATED BLOOD PRESSURE	AMLODIPINE BESILATE
146	CALCIUM CHANNEL BLOCKERS	ESSENTIAL HYPERTENSION	AMLODIPINE
147	CALCIUM CHANNEL BLOCKERS	ESSENTIAL HYPERTENSION	AMLODIPINE BESILATE
148	CALCIUM CHANNEL BLOCKERS	ESSENTIAL HYPERTENSION	FELODIPINE
149	CALCIUM CHANNEL BLOCKERS	ESSENTIAL PRIMARY HYPERTENSION	AMLODIPINE
150	CALCIUM CHANNEL BLOCKERS	HIGH BLOOD PRESSURE	AMLODIPINE
151	CALCIUM CHANNEL BLOCKERS	HTN	AMLODIPINE
152	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	AMLODIPINE
153	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	AMLODIPINE BESILATE
154	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	BARNIDIPINE HYDROCHLORIDE
155	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	DILTIAZEM
156	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	DILTIAZEM HYDROCHLORIDE
157	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	FELODIPINE
158	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	NIFEDIPINE
159	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	VERAPAMIL
160	CALCIUM CHANNEL BLOCKERS	HYPERTENSION (ESSENTIAL/PRIMARY)	VERAPAMIL HYDROCHLORIDE
161	CALCIUM CHANNEL BLOCKERS	HYPERTENSION ESSENTIAL	FELODIPINE
162	CALCIUM CHANNEL BLOCKERS	HYPERTNESION	AMLODIPINE BESILATE
163	CALCIUM CHANNEL BLOCKERS	HYPTERTENSION	AMLODIPINE
164	CALCIUM CHANNEL BLOCKERS	PRESTUDY HYPERTENSION	AMLODIPINE
165	CALCIUM CHANNEL BLOCKERS	SECONDARY STROKE PREVENTION	AMLODIPINE
166	CALCIUM CHANNEL BLOCKERS	SICK SINUS SYNDROME	VERAPAMIL

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
167	CALCIUM CHANNEL BLOCKERS	WORSENING OF HYPERTENSION	AMLODIPINE
168	CARDIAC THERAPY	HYPERTENSION	UBIDECARENONE
169	DIURETICS	ARTERIAL HYPERTENSION	HYDROCHLOROTHIAZIDE
170	DIURETICS	BENIGN ESSENTIAL HYPERTENSION	HYDROCHLOROTHIAZIDE
171	DIURETICS	BORDERLINE HYPERTENSION	HYDROCHLOROTHIAZIDE
172	DIURETICS	DIURETIC	FUROSEMIDE
173	DIURETICS	ELEVATED BLOOD PRESSURE READING, WITHOUT DIAGNOSIS OF HYPERTENSION	HYDROCHLOROTHIAZIDE
174	DIURETICS	ESSENTIAL HYPERTENSION	FUROSEMIDE
175	DIURETICS	ESSENTIAL HYPERTENSION	HYDROCHLOROTHIAZIDE
176	DIURETICS	HIGH BLOOD PRESSURE	HYDROCHLOROTHIAZIDE
177	DIURETICS	HYPERTENSION	AMILORIDE
178	DIURETICS	HYPERTENSION	BUMETANIDE
179	DIURETICS	HYPERTENSION	CHLORTALIDONE
180	DIURETICS	HYPERTENSION	DYAZIDE
181	DIURETICS	HYPERTENSION	FUROSEMIDE
182	DIURETICS	HYPERTENSION	HYDROCHLOROTHIAZIDE
183	DIURETICS	HYPERTENSION	INDAPAMIDE
184	DIURETICS	HYPERTENSION	MODURETIC
185	DIURETICS	HYPERTENSION	SPIRONOLACTONE
186	DIURETICS	HYPERTENSION	TRIAMTERENE
187	DIURETICS	HYPERTENSION, BENIGN	HYDROCHLOROTHIAZIDE
188	DIURETICS	HYPERTENTION	HYDROCHLOROTHIAZIDE
189	DIURETICS	WORSENING HYPERTENSION	HYDROCHLOROTHIAZIDE
190	LIPID MODIFYING AGENTS	HIGH BLOOD PRESSURE	PRAVASTATIN
191	LIPID MODIFYING AGENTS	HIGH BLOOD PRESSURE	PRAVASTATIN SODIUM

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
Diabetes Mellitus (DIABETES)			
1	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	DIABETES MELLITUS TYPE II	LISINOPRIL
2	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	TYPE 2 DIABETES	LISINOPRIL
3	ANTIHYPERTENSIVES	UNCONTROLLED DIABETES MELLITUS 2	CLONIDINE HYDROCHLORIDE
4	ANTIHYPERTENSIVES	UNCONTROLLED DIABETES MELLITUS 2	HYDRALAZINE HYDROCHLORIDE
5	BETA BLOCKING AGENTS	TYPE 2 DIABETES	METOPROLOL TARTRATE
6	DRUGS USED IN DIABETES	BORDERLINE DIABETES	METFORMIN
7	DRUGS USED IN DIABETES	DIABETES	DULAGLUTIDE
8	DRUGS USED IN DIABETES	DIABETES	GLIBENCLAMIDE
9	DRUGS USED IN DIABETES	DIABETES	GLICLAZIDE
10	DRUGS USED IN DIABETES	DIABETES	GLIMEPIRIDE
11	DRUGS USED IN DIABETES	DIABETES	GLIPIZIDE
12	DRUGS USED IN DIABETES	DIABETES	HUMAN MIXTARD
13	DRUGS USED IN DIABETES	DIABETES	INSULIN
14	DRUGS USED IN DIABETES	DIABETES	INSULIN ASPART
15	DRUGS USED IN DIABETES	DIABETES	INSULIN DETEMIR
16	DRUGS USED IN DIABETES	DIABETES	INSULIN GLARGINE
17	DRUGS USED IN DIABETES	DIABETES	INSULIN HUMAN
18	DRUGS USED IN DIABETES	DIABETES	INSULIN LISPRO
19	DRUGS USED IN DIABETES	DIABETES	METAGLIP
20	DRUGS USED IN DIABETES	DIABETES	METFORMIN
21	DRUGS USED IN DIABETES	DIABETES	METFORMIN HYDROCHLORIDE
22	DRUGS USED IN DIABETES	DIABETES	PIOGLITAZONE
23	DRUGS USED IN DIABETES	DIABETES	PIOGLITAZONE HYDROCHLORIDE
24	DRUGS USED IN DIABETES	DIABETES	SITAGLIPTIN
25	DRUGS USED IN DIABETES	DIABETES TYPE I	INSULIN GLARGINE
26	DRUGS USED IN DIABETES	DIABETES TYPE I	INSULIN LISPRO
27	DRUGS USED IN DIABETES	DIABETES 2	GLICLAZIDE
28	DRUGS USED IN DIABETES	DIABETES II	METFORMIN
29	DRUGS USED IN DIABETES	DIABETES KETOACIDOSIS	INSULIN
30	DRUGS USED IN DIABETES	DIABETES MELL. TYPE 2	INSULIN DETEMIR
31	DRUGS USED IN DIABETES	DIABETES MELL. TYPE 2	INSULIN LISPRO

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
32	DRUGS USED IN DIABETES	DIABETES MELL. TYPE 2	METFORMIN
33	DRUGS USED IN DIABETES	DIABETES MELLITIS TYPE 2	EMPAGLIFLOZIN
34	DRUGS USED IN DIABETES	DIABETES MELLITIS TYPE 2	GLIBENCLAMIDE
35	DRUGS USED IN DIABETES	DIABETES MELLITIS TYPE 2	INSULIN DETEMIR
36	DRUGS USED IN DIABETES	DIABETES MELLITIS TYPE 2	INSULIN LISPRO
37	DRUGS USED IN DIABETES	DIABETES MELLITUS	DULAGLUTIDE
38	DRUGS USED IN DIABETES	DIABETES MELLITUS	EXENATIDE
39	DRUGS USED IN DIABETES	DIABETES MELLITUS	GLIPIZIDE
40	DRUGS USED IN DIABETES	DIABETES MELLITUS	HUMAN MIXTARD
41	DRUGS USED IN DIABETES	DIABETES MELLITUS	INSULIN ASPART
42	DRUGS USED IN DIABETES	DIABETES MELLITUS	INSULIN DETEMIR
43	DRUGS USED IN DIABETES	DIABETES MELLITUS	INSULIN GLARGINE
44	DRUGS USED IN DIABETES	DIABETES MELLITUS	INSULIN HUMAN
45	DRUGS USED IN DIABETES	DIABETES MELLITUS	INSULIN LISPRO
46	DRUGS USED IN DIABETES	DIABETES MELLITUS	LIRAGLUTIDE
47	DRUGS USED IN DIABETES	DIABETES MELLITUS	METFORMIN
48	DRUGS USED IN DIABETES	DIABETES MELLITUS	METFORMIN HYDROCHLORIDE
49	DRUGS USED IN DIABETES	DIABETES MELLITUS	RISTFOR
50	DRUGS USED IN DIABETES	DIABETES MELLITUS	SITAGLIPTIN PHOSPHATE
51	DRUGS USED IN DIABETES	DIABETES MELLITUS TYP II	INSULIN LISPRO
52	DRUGS USED IN DIABETES	DIABETES MELLITUS TYP II	VELMETIA
53	DRUGS USED IN DIABETES	DIABETES MELLITUS 1	INSULIN GLARGINE
54	DRUGS USED IN DIABETES	DIABETES MELLITUS 1	INSULIN LISPRO
55	DRUGS USED IN DIABETES	DIABETES MELLITUS 11	GLIPIZIDE
56	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	CANAGLIFLOZIN
57	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	DULAGLUTIDE
58	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	EXENATIDE
59	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	GLIBOMET
60	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	GLIMEPIRIDE
61	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	GLIPIZIDE
62	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	HUMAN MIXTARD
63	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	INSULIN ASPART
64	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	INSULIN DETEMIR
65	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	INSULIN GLARGINE
66	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	METFORMIN

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
67	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	METFORMIN HYDROCHLORIDE
68	DRUGS USED IN DIABETES	DIABETES MELLITUS II	GLIPIZIDE
69	DRUGS USED IN DIABETES	DIABETES MELLITUS II	METFORMIN
70	DRUGS USED IN DIABETES	DIABETES MELLITUS II	SITAGLIPTIN
71	DRUGS USED IN DIABETES	DIABETES MELLITUS TYP 2	METFORMIN
72	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	GLIPIZIDE
73	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	INSULIN GLARGINE
74	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	INSULIN LISPRO
75	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	METFORMIN
76	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	METFORMIN HYDROCHLORIDE
77	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	SITAGLIPTIN PHOSPHATE
78	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	CANAGLIFLOZIN W/METFORMIN HYDROCHLORIDE
79	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	DULAGLUTIDE
80	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	GLIPIZIDE
81	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	HUMAN MIXTARD
82	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	INSULIN
83	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	INSULIN ASPART
84	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	INSULIN DETEMIR
85	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	INSULIN GLARGINE
86	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	INSULIN LISPRO
87	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	METFORMIN
88	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	METFORMIN HYDROCHLORIDE
89	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	NATEGLINIDE
90	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	SITAGLIPTIN PHOSPHATE
91	DRUGS USED IN DIABETES	DIABETES MELLITUS, TYPE II	METFORMIN HYDROCHLORIDE
92	DRUGS USED IN DIABETES	DIABETES TYPE 2	GLIPIZIDE
93	DRUGS USED IN DIABETES	DIABETES TYPE 2	HUMAN MIXTARD
94	DRUGS USED IN DIABETES	DIABETES TYPE 2	INSULIN ASPART
95	DRUGS USED IN DIABETES	DIABETES TYPE 2	INSULIN DETEMIR
96	DRUGS USED IN DIABETES	DIABETES TYPE 2	INSULIN GLARGINE
97	DRUGS USED IN DIABETES	DIABETES TYPE 2	INSULIN LISPRO
98	DRUGS USED IN DIABETES	DIABETES TYPE 2	KOMBIGLYZE
99	DRUGS USED IN DIABETES	DIABETES TYPE 2	METFORMIN
100	DRUGS USED IN DIABETES	DIABETES TYPE 2	SITAGLIPTIN PHOSPHATE

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
101	DRUGS USED IN DIABETES	DIABETES TYPE II	METFORMIN
102	DRUGS USED IN DIABETES	DIABETES, TYPE 2	GLIMEPIRIDE
103	DRUGS USED IN DIABETES	DIABETES, TYPE 2	LIRAGLUTIDE
104	DRUGS USED IN DIABETES	DIABETES, TYPE 2	PIOGLITAZONE
105	DRUGS USED IN DIABETES	DIABETIS	INSULIN GLARGINE
106	DRUGS USED IN DIABETES	DM2	GLIPIZIDE
107	DRUGS USED IN DIABETES	DM2	METFORMIN HYDROCHLORIDE
108	DRUGS USED IN DIABETES	HYPERGLICEMIA	GLIPIZIDE
109	DRUGS USED IN DIABETES	HYPERGLYCEMIA	INSULIN HUMAN
110	DRUGS USED IN DIABETES	HYPERGLYCEMIA	METFORMIN
111	DRUGS USED IN DIABETES	HYPERGLYCEMIA	METFORMIN HYDROCHLORIDE
112	DRUGS USED IN DIABETES	HYPERINSULINISM	METFORMIN
113	DRUGS USED IN DIABETES	HYPERTENSION	METFORMIN
114	DRUGS USED IN DIABETES	NONALCOHOLIC STEATOHEPATITIS	METFORMIN
115	DRUGS USED IN DIABETES	TYPE 1 DIABETES	INSULIN DEGLUDEC
116	DRUGS USED IN DIABETES	TYPE 1 DIABETES MELLITUS	INSULIN ASPART
117	DRUGS USED IN DIABETES	TYPE 1 DIABETES MELLITUS	INSULIN GLARGINE
118	DRUGS USED IN DIABETES	TYPE 2 DIABETES	GLICLAZIDE
119	DRUGS USED IN DIABETES	TYPE 2 DIABETES	HUMAN MIXTARD
120	DRUGS USED IN DIABETES	TYPE 2 DIABETES	INSULIN ASPART
121	DRUGS USED IN DIABETES	TYPE 2 DIABETES	INSULIN GLARGINE
122	DRUGS USED IN DIABETES	TYPE 2 DIABETES	INSULIN LISPRO
123	DRUGS USED IN DIABETES	TYPE 2 DIABETES	METFORMIN
124	DRUGS USED IN DIABETES	TYPE 2 DIABETES	METFORMIN HYDROCHLORIDE
125	DRUGS USED IN DIABETES	TYPE 2 DIABETES	SITAGLIPTIN PHOSPHATE
126	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	GLIMEPIRIDE
127	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	HUMAN MIXTARD
128	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	INSULIN HUMAN
129	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	LIRAGLUTIDE
130	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	METFORMIN HYDROCHLORIDE
131	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	PIOGLITAZONE
132	DRUGS USED IN DIABETES	TYPE II DIABETES	CANAGLIFLOZIN W/METFORMIN HYDROCHLORIDE
133	DRUGS USED IN DIABETES	TYPE II DIABETES	DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE W/METFO

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
134	DRUGS USED IN DIABETES	TYPE II DIABETES	GLIPIZIDE
135	DRUGS USED IN DIABETES	TYPE II DIABETES	INSULIN
136	DRUGS USED IN DIABETES	TYPE II DIABETES	INSULIN DETEMIR
137	DRUGS USED IN DIABETES	TYPE II DIABETES	INSULIN GLARGINE
138	DRUGS USED IN DIABETES	TYPE II DIABETES	LIRAGLUTIDE
139	DRUGS USED IN DIABETES	TYPE II DIABETES	METFORMIN
140	DRUGS USED IN DIABETES	TYPE II DIABETES	SITAGLIPTIN PHOSPHATE
141	DRUGS USED IN DIABETES	TYPE II DIABETES MELLITUS	EXENATIDE
142	DRUGS USED IN DIABETES	TYPE II DIABETES MELLITUS	METFORMIN
143	DRUGS USED IN DIABETES	TYPE II DIABETES MELLITUS	METFORMIN HYDROCHLORIDE
144	DRUGS USED IN DIABETES	UNCONTROLLED DIABETES MELLITUS 2	INSULIN LISPRO
145	DRUGS USED IN DIABETES	UNCONTROLLED DIABETES MELLITUS WITH HYPERGLICEMIA	GLIPIZIDE
146	DRUGS USED IN DIABETES	UNCONTROLLED DIABETES MELLITUS WITH HYPERGLICEMIA	HUMAN MIXTARD
147	DRUGS USED IN DIABETES	UNCONTROLLED DM2	INSULIN DETEMIR
148	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	HERBAL SUPPLEMENT	GLYCINE MAX EXTRACT
149	LIPID MODIFYING AGENTS	DIABETES MELLITUS TYPE II	PRAVASTATIN

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
Cardiovascular (CARDDIS)			
1	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ACUTE MYOCARDIAL INFARCTION	IRBESARTAN
2	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	CARDIOMYOPATHY	LISINOPRIL
3	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	CARDIOMYOPATHY	RAMIPRIL
4	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	CONGESTIVE HEART FAILURE	LISINOPRIL
5	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	CORONARY ARTERY DISEASE	RAMIPRIL
6	BETA BLOCKING AGENTS	ACUTE MYOCARDIAL INFARCTION	BISOPROLOL FUMARATE
7	BETA BLOCKING AGENTS	ANTI ARRHYTHMIC	SOTALOL
8	BETA BLOCKING AGENTS	ATHEROSCLEROTIC HEART DISEASE OF NATIVE CORONARY ARTERY WITHOUT ANGINA PECTORIS	CARVEDILOL
9	BETA BLOCKING AGENTS	ATRIAL FIBRILATION	ATENOLOL
10	BETA BLOCKING AGENTS	ATRIAL FIBRILATION	METOPROLOL
11	BETA BLOCKING AGENTS	ATRIAL FIBRILLATION	METOPROLOL
12	BETA BLOCKING AGENTS	ATRIAL FIBRILLATION	METOPROLOL TARTRATE
13	BETA BLOCKING AGENTS	ATYPICAL CHEST PAIN	LABETALOL
14	BETA BLOCKING AGENTS	BRUGADA SYNDROME	BISOPROLOL
15	BETA BLOCKING AGENTS	CAD	METOPROLOL SUCCINATE
16	BETA BLOCKING AGENTS	CADRIOMYOPATHY	BISOPROLOL
17	BETA BLOCKING AGENTS	CARDIAC PACEMAKER INSITU	METOPROLOL
18	BETA BLOCKING AGENTS	CARDIAC PROPHYLAXIS	CARVEDILOL
19	BETA BLOCKING AGENTS	CARDIOMYOPATHY	CARVEDILOL
20	BETA BLOCKING AGENTS	CHEST TIGHTNESS	BISOPROLOL
21	BETA BLOCKING AGENTS	CONGESTIVE HEART FAILURE	ATENOLOL
22	BETA BLOCKING AGENTS	CONGESTIVE HEART FAILURE	CARVEDILOL
23	BETA BLOCKING AGENTS	CONTROLLED HYPERTENSION	TENORETIC
24	BETA BLOCKING AGENTS	CORONARY ARTERY DISEASE	METOPROLOL
25	BETA BLOCKING AGENTS	CORONARY ARTERY DISEASE	METOPROLOL SUCCINATE
26	BETA BLOCKING AGENTS	CORONARY ARTERY STENOSIS	METOPROLOL
27	BETA BLOCKING AGENTS	DYSRHYTHMIA	BISOPROLOL FUMARATE
28	BETA BLOCKING AGENTS	HEART FAILURE AND HYPERTENSION	CARVEDILOL
29	BETA BLOCKING AGENTS	INTERMITTENT ARRHYTHMIA	BISOPROLOL
30	BETA BLOCKING AGENTS	MITRAL INSUFFICIENCY	BISOPROLOL

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
31	BETA BLOCKING AGENTS	PREVENTATIVE FOLLOWING ACUTE MYCARDIAL INFARCTION	BISOPROLOL
32	BETA BLOCKING AGENTS	SICK SINUS SYNDROME	METOPROLOL
33	BETA BLOCKING AGENTS	SUPRA VENTRICULAR TACHYCARDIA	ATENOLOL
34	BETA BLOCKING AGENTS	SUPRAVENTRICULAR TACHYCARDIA	ATENOLOL
35	BETA BLOCKING AGENTS	SUPRAVENTRICULAR TACHYCARDIA	METOPROLOL
36	BETA BLOCKING AGENTS	TACHYCARDIA	ATENOLOL
37	CALCIUM CHANNEL BLOCKERS	CORONARY ARTERY DISEASE	AMLODIPINE
38	CALCIUM CHANNEL BLOCKERS	CORONARY ARTERY DISEASE	AMLODIPINE BESILATE
39	CALCIUM CHANNEL BLOCKERS	SUPRAVENTRICULAR TACHYCARDIA	VERAPAMIL
40	CARDIAC THERAPY	ACUTE MYOCARDIAL INFARCTION	AMIODARONE HYDROCHLORIDE
41	CARDIAC THERAPY	ACUTE MYOCARDIAL INFARCTION	ISOSORBIDE DINITRATE
42	CARDIAC THERAPY	ALLERGIC REACTION	EPINEPHRINE
43	CARDIAC THERAPY	ANGINA	GLYCERYL TRINITRATE
44	CARDIAC THERAPY	ANGINA PECTORIS	RANOLAZINE
45	CARDIAC THERAPY	ANGIOGRAM/STENT	ADENOSINE
46	CARDIAC THERAPY	ANGIONEUROTIC EDEMA	EPINEPHRINE
47	CARDIAC THERAPY	ANTIARRHYTHMIC AGENT	FLECAINIDE ACETATE
48	CARDIAC THERAPY	ATRIAL FIBRILLATION	DIGOXIN
49	CARDIAC THERAPY	ATRIAL FIBRILLATION	FLECAINIDE ACETATE
50	CARDIAC THERAPY	ATYPICAL CHEST PAIN	GLYCERYL TRINITRATE
51	CARDIAC THERAPY	CAD	UBIDECARENONE
52	CARDIAC THERAPY	CARDIOMYOPATHY	ISOSORBIDE DINITRATE
53	CARDIAC THERAPY	CARDIOVASCULAR DISEASE PROPHYLAXIS	UBIDECARENONE
54	CARDIAC THERAPY	CHEST PAIN	GLYCERYL TRINITRATE
55	CARDIAC THERAPY	CHEST PAINS	GLYCERYL TRINITRATE
56	CARDIAC THERAPY	CHESTPAIN	GLYCERYL TRINITRATE
57	CARDIAC THERAPY	CORONARY ARTERY DISEASE	GLYCERYL TRINITRATE
58	CARDIAC THERAPY	CORONARY ARTERY DISEASE	ISOSORBIDE MONONITRATE
59	CARDIAC THERAPY	HYPERLIPIDEMIA	ISOSORBIDE MONONITRATE
60	CARDIAC THERAPY	NSTEMI	ISOSORBIDE DINITRATE
61	CARDIAC THERAPY	PERIOP STRESS TEST	REGADENOSON
62	CARDIAC THERAPY	PROPHYLAXIS	GLYCERYL TRINITRATE
63	CARDIAC THERAPY	PROPHYLAXIS FOR CARDIAC HEALTH	UBIDECARENONE

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
64	CARDIAC THERAPY	SUPRAVENTRICULAR TACHYCARDIA	ADENOSINE
65	CARDIAC THERAPY	UNCONTROLLED DIABETES MELLITUS 2	AMIODARONE HYDROCHLORIDE
66	CARDIAC THERAPY	UNCONTROLLED DIABETES MELLITUS 2	GLYCERYL TRINITRATE
67	DIURETICS	ACUTE RESPIRATORY FAILURE	FUROSEMIDE
68	DIURETICS	AORTIC VALVE REPLACEMENT	FUROSEMIDE
69	DIURETICS	CHF	BUMETANIDE
70	DIURETICS	CHF	HYDROCHLOROTHIAZIDE
71	DIURETICS	CHF	METOLAZONE
72	DIURETICS	CONGESTIVE HEART FAILURE	BUMETANIDE
73	DIURETICS	CONGESTIVE HEART FAILURE	FUROSEMIDE
74	DIURETICS	CONGESTIVE HEART FAILURE	HYDROCHLOROTHIAZIDE
75	DIURETICS	CONGESTIVE HEART FAILURE	METOLAZONE
76	DIURETICS	CONGESTIVE HEART FAILURE	SPIRONOLACTONE
77	DIURETICS	CORONARY ARTERY DISEASE	HYDROCHLOROTHIAZIDE
78	DIURETICS	CORONARY ARTERY DISEASE.	FUROSEMIDE
79	DIURETICS	ELEVATION OF BLOOD PRESSURE	FUROSEMIDE
80	DIURETICS	MITRAL INSUFFICIENCY	TORASEMIDE
81	DIURETICS	TRANSGENGER	SPIRONOLACTONE
82	LIPID MODIFYING AGENTS	ACUTE MYOCARDIAL INFARCTION	ATORVASTATIN CALCIUM
83	LIPID MODIFYING AGENTS	ACUTE MYOCARDIAL INFARCTION	OMEGA 3 TRIGLYCERIDES
84	LIPID MODIFYING AGENTS	ATHEROSCLEROTIC HEART DISEASE OF NATIVE CORONARY ARTERY WITHOUT ANGINA PECTORIS	SIMVASTATIN
85	LIPID MODIFYING AGENTS	BASILAR ARTERY THROMBUS	ATORVASTATIN CALCIUM
86	LIPID MODIFYING AGENTS	CAD	PRAVASTATIN SODIUM
87	LIPID MODIFYING AGENTS	CAD	ROSUVASTATIN CALCIUM
88	LIPID MODIFYING AGENTS	CARDIAC PROPHYLAXIS	ATORVASTATIN
89	LIPID MODIFYING AGENTS	CARDIAC PROPHYLAXIS	FISH OIL
90	LIPID MODIFYING AGENTS	CARDIOVASCULAR PROPHYLAXIS	ATORVASTATIN CALCIUM
91	LIPID MODIFYING AGENTS	CHEST TIGHTNESS	ATORVASTATIN

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
Hyperlipidemia (HLIPDEM)			
1	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HYPERTRIGLYCERIDEMIA	LISINOPRIL
2	ANTIHYPERTENSIVES	HYPERCHOLESTEROLEMIA	DOXAZOSIN MESILATE
3	CARDIAC THERAPY	HYPERCHOLESTEROLEMIA	UBIDECARENONE
4	LIPID MODIFYING AGENTS	ABNORMAL LIPIDS	ATORVASTATIN
5	LIPID MODIFYING AGENTS	CARDIAC PROPHYLAXIS	ROSUVASTATIN
6	LIPID MODIFYING AGENTS	CHOLESTEROL	ROSUVASTATIN
7	LIPID MODIFYING AGENTS	CHOLESTEROL	ROSUVASTATIN CALCIUM
8	LIPID MODIFYING AGENTS	CHOLESTEROLEAMIA	ATORVASTATIN
9	LIPID MODIFYING AGENTS	CHOLESTERORL	ROSUVASTATIN CALCIUM
10	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE	ATORVASTATIN
11	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE	EZETIMIBE
12	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE	FENOFIBRATE
13	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE	ROSUVASTATIN CALCIUM
14	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE PROPHYLAXIS	ATORVASTATIN
15	LIPID MODIFYING AGENTS	DIET SUPPLEMENT	FISH OIL
16	LIPID MODIFYING AGENTS	DIETARY SUPPLEMENT	FISH OIL
17	LIPID MODIFYING AGENTS	DIETARY SUPPLEMENTS	FISH OIL
18	LIPID MODIFYING AGENTS	DYSLIPEDEMIA	ROSUVASTATIN CALCIUM
19	LIPID MODIFYING AGENTS	DYSLIPIDAEMIA	ATORVASTATIN
20	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	ATORVASTATIN
21	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	FENOFIBRATE
22	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	FISH OIL
23	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	GEMFIBROZIL
24	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	PRAVASTATIN
25	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	ROSUVASTATIN
26	LIPID MODIFYING AGENTS	DYSLIPIDEMIA, WORSENING	ROSUVASTATIN
27	LIPID MODIFYING AGENTS	DYSLIPIDERMIA	PRAVASTATIN

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
28	LIPID MODIFYING AGENTS	ELEVATED CHOLESTEROL	SIMVASTATIN
29	LIPID MODIFYING AGENTS	ELEVATED LIPIDS	ATORVASTATIN
30	LIPID MODIFYING AGENTS	ELEVATED LIPIDS	ATORVASTATIN CALCIUM
31	LIPID MODIFYING AGENTS	ELEVATED TRIGLYCERIDES	FISH OIL
32	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	ATORVASTATIN
33	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	ATORVASTATIN CALCIUM
34	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	GEMFIBROZIL
35	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	LOVASTATIN
36	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	PRAVASTATIN
37	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	ROSUVASTATIN CALCIUM
38	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	SIMVASTATIN
39	LIPID MODIFYING AGENTS	HIGH CHOLESTROL	ATORVASTATIN
40	LIPID MODIFYING AGENTS	HIGH PLASMA LIPIDS	ATORVASTATIN
41	LIPID MODIFYING AGENTS	HIGH TRIGLYCERIDES	FENOFIBRATE
42	LIPID MODIFYING AGENTS	HIGH TRIGLYCERIDES AND HYPERCHOLESTEROLEMIA	ATORVASTATIN
43	LIPID MODIFYING AGENTS	HIPERCOLESTEROLEMIA	ATORVASTATIN
44	LIPID MODIFYING AGENTS	HIPERCOLESTEROLEMIA	ATORVASTATIN CALCIUM
45	LIPID MODIFYING AGENTS	HIPERCOLESTEROLEMIA	SIMVASTATIN
46	LIPID MODIFYING AGENTS	HYERLIPIDEMIA	OMEGA-3-ACID ETHYL ESTER
47	LIPID MODIFYING AGENTS	HYPERCHOLESTERIMIA	FENOFIBRATE
48	LIPID MODIFYING AGENTS	HYPERCHOLESTERINAEMIA	ATORVASTATIN
49	LIPID MODIFYING AGENTS	HYPERCHOLESTERINAEMIA	PRAVASTATIN
50	LIPID MODIFYING AGENTS	HYPERCHOLESTERINEMIA	PRAVASTATIN
51	LIPID MODIFYING AGENTS	HYPERCHOLESTERINEMIA	SIMVASTATIN
52	LIPID MODIFYING AGENTS	HYPERCHOLESTEROL	PRAVASTATIN
53	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLAEMIA	ATORVASTATIN
54	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLAEMIA	PRAVASTATIN
55	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLAEMIA	ROSUVASTATIN
56	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLAEMIA	SIMVASTATIN
57	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	ATORVASTATIN
58	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	ATORVASTATIN CALCIUM

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
59	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	EZETIMIBE
60	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	FENOFIBRATE
61	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	FISH OIL
62	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	LOVASTATIN
63	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	PITAVASTATIN CALCIUM
64	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	PRAVASTATIN
65	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	PRAVASTATIN SODIUM
66	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	ROSUVASTATIN
67	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	ROSUVASTATIN CALCIUM
68	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	SIMVASTATIN
69	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA (PURE) AND MIXED HYPERLIPIDEMIA	ROSUVASTATIN CALCIUM
70	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLMIA	PRAVASTATIN SODIUM
71	LIPID MODIFYING AGENTS	HYPERCHOLESTROLEMIA	ATORVASTATIN
72	LIPID MODIFYING AGENTS	HYPERCHOLESTROLEMIA	ATORVASTATIN CALCIUM
73	LIPID MODIFYING AGENTS	HYPERCHOLESTROLEMIA	FENOFIBRATE
74	LIPID MODIFYING AGENTS	HYPERCHOLSTEROAEMIA	ATORVASTATIN CALCIUM
75	LIPID MODIFYING AGENTS	HYPERCOLESTEROLEMIA	SIMVASTATIN
76	LIPID MODIFYING AGENTS	HYPERLIDEMIA	ROSUVASTATIN CALCIUM
77	LIPID MODIFYING AGENTS	HYPERLIDIPEMIA	ATORVASTATIN
78	LIPID MODIFYING AGENTS	HYPERLIPDEMIA	ROSUVASTATIN CALCIUM
79	LIPID MODIFYING AGENTS	HYPERLIPEDMIA-MIXED	ATORVASTATIN
80	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	ATORVASTATIN
81	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	FENOFIBRATE
82	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	PRAVASTATIN
83	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	PRAVASTATIN SODIUM
84	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	ROSUVASTATIN
85	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	ROSUVASTATIN CALCIUM
86	LIPID MODIFYING AGENTS	HYPERLIPIDEMA	ATORVASTATIN
87	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	ATORVASTATIN
88	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	ATORVASTATIN CALCIUM
89	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	COLESEVELAM HYDROCHLORIDE

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
90	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	EICOSAPENTAENOIC ACID ETHYL ESTER
91	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	EZETIMIBE
92	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	FENOFIBRATE
93	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	FENOFIBRIC ACID
94	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	FISH OIL
95	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	GEMFIBROZIL
96	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	LOVASTATIN
97	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	OMEGA-3-ACID ETHYL ESTER
98	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	PELAGO
99	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	PRAVASTATIN
100	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	PRAVASTATIN SODIUM
101	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	ROSUVASTATIN
102	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	ROSUVASTATIN CALCIUM
103	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	SIMVASTATIN
104	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA PREVENTION	ROSUVASTATIN CALCIUM
105	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA,	PRAVASTATIN
106	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA, MIXED	ATORVASTATIN CALCIUM
107	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA, MIXED	FENOFIBRATE
108	LIPID MODIFYING AGENTS	HYPERTENSION	ATORVASTATIN
109	LIPID MODIFYING AGENTS	HYPERTENSION	PRAVASTATIN
110	LIPID MODIFYING AGENTS	HYPERTRIGLYCERDEMIA	ATORVASTATIN
111	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	ATORVASTATIN CALCIUM
112	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	FENOFIBRATE
113	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	FENOFIBRIC ACID
114	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	FIBRATES
115	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	FISH OIL
116	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	OMEGA-3 TRIGLYCERIDES
117	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	PRAVASTATIN
118	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA,HYPERCHOLESTEROLEMIA	ATORVASTATIN
119	LIPID MODIFYING AGENTS	HYPERTRIGLYERIDEMIA	GEMFIBROZIL

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
120	LIPID MODIFYING AGENTS	HYPERTRYGLYCERIDEMIA	PRAVASTATIN
121	LIPID MODIFYING AGENTS	INDICATION HYPERLIPIDEMIA	FENOFIBRATE
122	LIPID MODIFYING AGENTS	IRRITABLE BOWEL SYNDROME	FISH OIL
123	LIPID MODIFYING AGENTS	ISCHEMIC HEART DISEASE	ROSUVASTATIN CALCIUM
124	LIPID MODIFYING AGENTS	LDL-CHOLESTEROL GRADE 3 ELEVATION	ROSUVASTATIN
125	LIPID MODIFYING AGENTS	MIXED DYSLIPIDEMIA	FENOFIBRATE
126	LIPID MODIFYING AGENTS	MIXED DYSLIPIDEMIA	ROSUVASTATIN CALCIUM
127	LIPID MODIFYING AGENTS	MIXED HYPERLIPDEMIA	ATORVASTATIN
128	LIPID MODIFYING AGENTS	MIXED HYPERLIPIDEMIA	ATORVASTATIN
129	LIPID MODIFYING AGENTS	MIXED HYPERLIPIDEMIA	FENOFIBRATE
130	LIPID MODIFYING AGENTS	MIXED HYPERLIPIDEMIA	GEMFIBROZIL
131	LIPID MODIFYING AGENTS	NUTRITION SUPPLEMENT	FISH OIL
132	LIPID MODIFYING AGENTS	NUTRITIONAL SUPPLEMENT	FISH OIL
133	LIPID MODIFYING AGENTS	NUTRITIONAL SUPPLEMENT	OMEGA-3 FATTY ACIDS
134	LIPID MODIFYING AGENTS	PREVENTATIVE FOLLOWING ACUTE MYCARDIAL INFARCTION	ATORVASTATIN
135	LIPID MODIFYING AGENTS	PREVENTION FOR HYPERCHOLESTEROLEMIA	OMEGA-3 FATTY ACIDS
136	LIPID MODIFYING AGENTS	PREVENTIVE	FISH OIL W/LINUM USITATISSIMUM SEED OIL
137	LIPID MODIFYING AGENTS	PROPHYLAXIS	FISH OIL
138	LIPID MODIFYING AGENTS	PURE HYPERCHOLESTEROLEMIA	ATORVASTATIN
139	LIPID MODIFYING AGENTS	SECONDARY STROKE PREVENTION	ATORVASTATIN
140	LIPID MODIFYING AGENTS	STROKE PROPHYLAXIS	ATORVASTATIN
141	LIPID MODIFYING AGENTS	SUPPLEMENT	FISH OIL
142	LIPID MODIFYING AGENTS	SUPPLEMENT	OMEGA 3 6 9
143	LIPID MODIFYING AGENTS	SUPPLEMENT	OMEGA-3 FATTY ACIDS
144	LIPID MODIFYING AGENTS	SUPPLEMENT	OMEGA-3 FATTY ACIDS W/OMEGA-6 FATTY ACIDS
145	LIPID MODIFYING AGENTS	SUPPLEMENT	OMEGA-3-ACID ETHYL ESTER

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
146	LIPID MODIFYING AGENTS	SUPPLEMENT/HYPERLIPIDEMIA	FISH OIL
147	LIPID MODIFYING AGENTS	SUPPLEMENTAL USE	FISH OIL
148	LIPID MODIFYING AGENTS	SUPPLEMETN	FISH OIL
149	LIPID MODIFYING AGENTS	UNCONTROLLED DIABETES MELLITUS 2	ATORVASTATIN
150	LIPID MODIFYING AGENTS	WORSENING HYPERLIPIDEMIA	ATORVASTATIN
151	LIPID MODIFYING AGENTS	WORSENING OF HYPERLIPIDEMIA	FISH OIL
152	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	NICOTINIC ACID
153	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	NICOTINIC ACID
154	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	NICOTINIC ACID
155	LIPID MODIFYING AGENTS	MIXED HYPERLIPIDEMIA	NICOTINIC ACID

Appendix 5. Alcohol Use Disorders Identification Test

Each question has a set of responses with each response having a score ranging from 0 to 4. The summation of all response scores provides the total score. If after data query, inconsistent responses are still present for questions that should have been skipped based on responses to previous questions, the most conservative (higher) score or response will be selected for each individual question as well as summation of the total score.

Questions	0	1	2	3	4
1. How often do you have a drink containing alcohol? (Skip to Questions 9 and 10 if Total Score for Question 1 = 0)	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7, 8, or 9	10 or more
3. How often do you have six or more drinks on one occasion? (Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0)	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected from you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured as a result of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10. Has a relative, friend, doctor, or another health worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year

Appendix 6. Efficacy Information from Truvada as PrEP in MSMs

Clinical Trial	Sample Size Placebo (PY Follow-Up)	Sample Size Truvada (PY Follow-Up)	HIV Infections (Incidence per 100 PY)		Rate Ratios in HIV Infection Rates, per 100 PY [95% CI]	Rate Difference in HIV Infection Rates, per 100 PY [95% CI]
			Placebo	Truvada		
PROUD	255 (222)	268 (243)	20 (9.0)	3 (1.2)	7.3 [2.2, 24.2]	7.8 [3.6, 12.0]
IPERGAY	201 (212)	199 (220)	14 (6.6)	2 (0.9)	7.3 [1.7, 31.6]	5.7 [2.0, 9.4]
iPrEX (URAI subgroup) at screening	753 (1054)	732 (1055)	56 (5.3)	23 (2.2)	2.4 [1.5, 3.9]	3.1 [1.5, 5.8]
Pool	1209 (1488)	1199 (1518)	90 {6.96}*	28 {**1.44**}*	5.1* [**2.64**, 9.70] NI Margin: **1.62**	5.5* [**3.60**, 7.47] NI Margin: **1.2**

Source: PROUD from {McCormack 2015}; IPERGAY from {Molina 2015}; iPrEx from {Grant 2010}
Note: The NI margins are based on the lower 95% CI bounds (LCB); to preserve 50% of Truvada effect vs Placebo (square root of LCB) for the rate ratio, and to preserve 67% of Truvada effect vs Placebo (1/3 of LCB) for the rate difference.
* The pooled incidence rate for placebo and F/TDF, based on equal weighting of three studies, are within {} which are used for estimating the rate ratio, and rate difference and their corresponding 95% CI.

Appendix 7. TFV-DP Simulations to Support On-Treatment HIV Infections Analysis

Simulation analyses were conducted to define the period of time participants in DISCOVER are expected to have PBMC-associated TFV-DP concentrations associated with HIV prevention after cessation of study drug (F/TAF 200/25 mg or F/TDF 200/300 mg) to support an on-treatment efficacy sensitivity analysis.

Briefly, TAF and TDF are distinct prodrugs of the active intracellular metabolite, TFV-DP, which has a long half-life {Hawkins 2005}. The median PBMC-associated concentration of TFV-DP expected to be associated with HIV prevention following once daily administration of F/TDF for PrEP based on data from the iPrEX study was ~40 fmol/10^6 cells {Anderson 2012b} As such, it is expected that PBMC-associated TFV-DP concentrations at or above this threshold will be associated with prevention of HIV-infection. Thus, the objective of this analysis was to define the period of time participants are expected to have TFV-DP concentrations $\geq$ 40 fmol/10^6 cells after cessation of F/TAF or F/TDF taken once daily in DISCOVER. The methodology and results of these analyses are described below.

Methodology

Studies Included in the Analysis

For the simulations of TFV-DP from TAF, PBMC-associated TFV-DP PK data was included from a Phase 1 study in healthy volunteers (GS-US-380-4017). In this study, PBMC samples for TFV-DP were collected following administration of bictegravir/F/TAF 50/200/25 mg once daily for 28 days (N 26). Samples for TFV-DP were collected over a period of 28 days postdose after the last dose of study drug. Mean (CV%) trough concentrations of TFV-DP from this study (434.0 [108.7] fmol/10^6 cells) were similar to those observed with historical data following administration of F/TAF (200/25 mg with unboosted ARV agents or 200/10 mg with boosted ARV agents) in HIV-infected participants in the Phase 3 Study GS-US-311-1089 (430.2 [114.1] fmol/10^6 cells).

For the simulations of TFV-DP from TDF, PBMC-associated TFV-DP PK data was included from a Phase 1 study in HIV-infected patients {Hawkins 2005}. In this study, HIV-infected participants who were on stable TDF 300 mg once daily-containing regimens discontinued TDF and switched to a non-NRTI or protease inhibitor. PBMC samples for TFV-DP were collected following discontinuation of TDF (N 8) over a period of 28 days postdose. While mean trough concentrations of TFV-DP from this study (76.4 [26.3] fmol/10^6 cells) were similar to those observed with historical data following administration of F/TDF 200/300 mg in HIV-infected participants in the Phase 3 Study GS-US-311-1089 (100.0 [139.0] fmol/10^6 cells), the variability was lower. This was accounted for in the simulations and is described further below.

Analysis Method

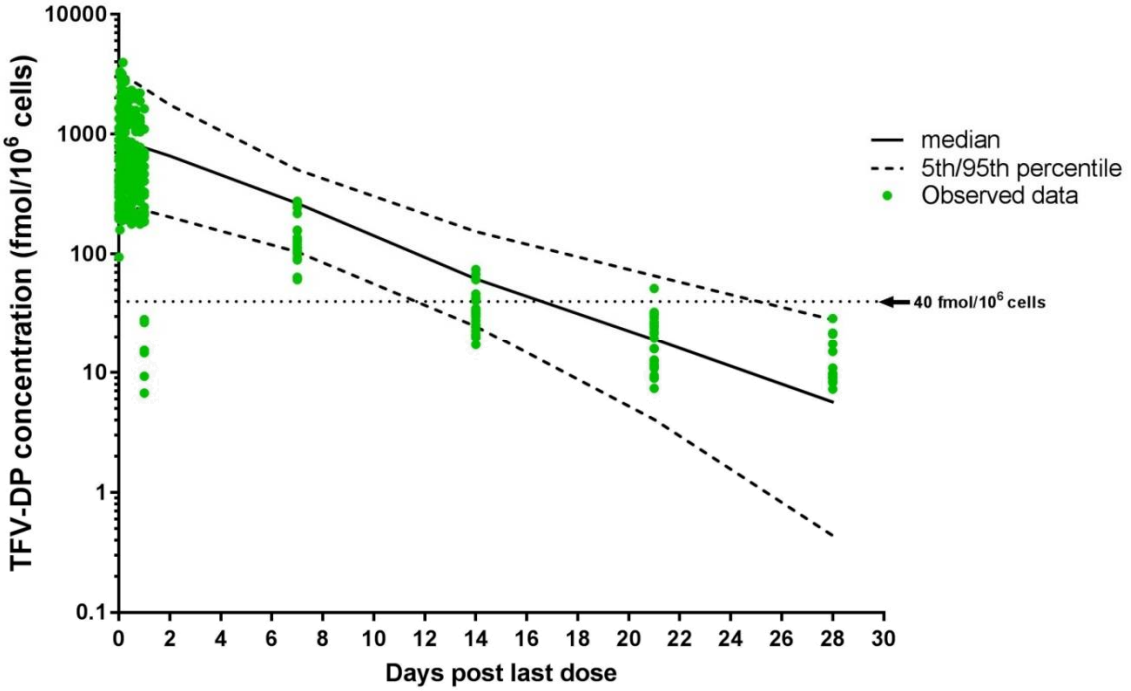
Observed TFV-DP concentration data from TAF or TDF was fit to a 1 compartment PK model with 1st order absorption and elimination, and no lag time, which was the 'best fit' based on comparison of Akaike information criterion (AIC) values with other models (ie., 2 compartment with or without lag time). The estimated slopes from the model were used to estimate half-life and simulate concentrations of TFV-DP over time following steady-state administration of either TAF 25 mg or TDF 300mg. Phoenix WinNonlin® 7.0. software was used for data fitting and simulations.

Results

TFV-DP from TAF

The median predicted half-life of TFV-DP (~100 hours) following steady-state administration of TAF 25 mg was similar to the observed value (~115 hours, N 26; Study GS-US-380-4017). Based on the median simulated TFV-DP concentration over time shown in Appendix Figure 1, participants (50th percentile and above) are expected to have TFV-DP concentrations ≥ 40 fmol/10^6 cells approximately 16 days after cessation of F/TAF 200/25 mg taken once daily.

Appendix Figure 1. Observed and Predicted PBMC-associated TFV-DP Concentrations with F/TAF 200/25 mg

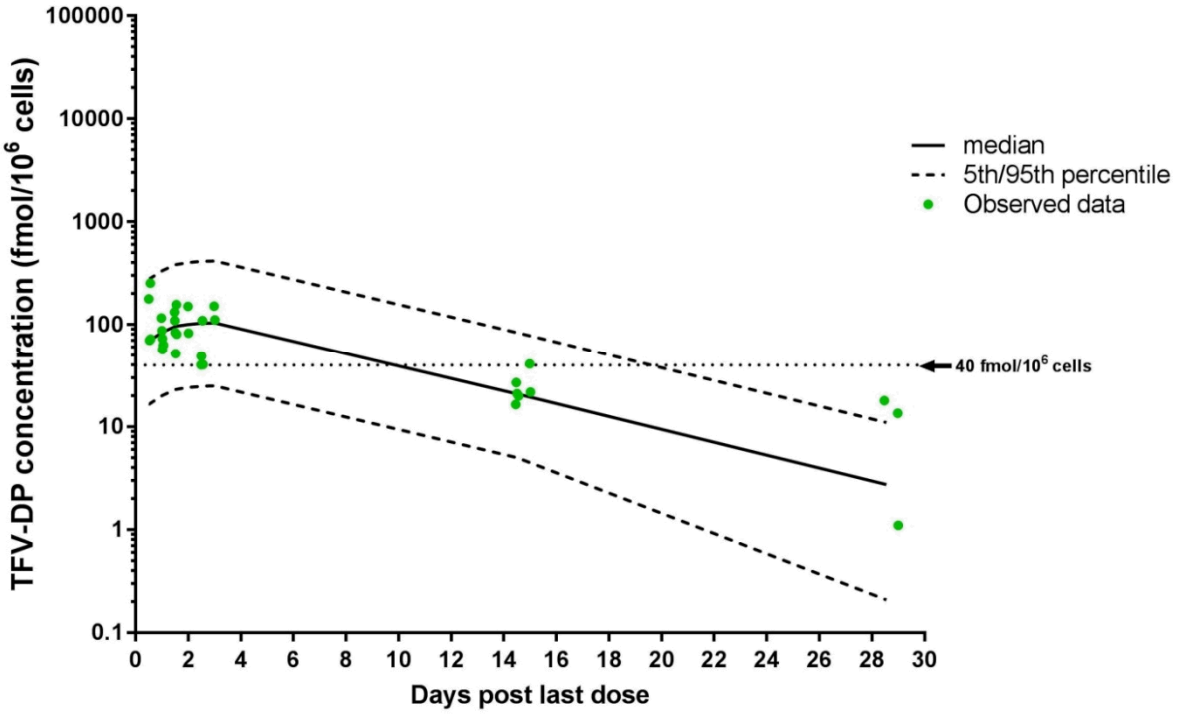


Green dots: Observed PBMC associated TFV DP concentrations after the last dose of bictegravir/F/TAF 50/200/25 mg once daily for 28 days from Study GS US 380 4017
Solid and dotted black lines: Simulated median and 5th and 95th percentiles of TFV DP concentrations over time
Horizontal dotted black line: Concentration of TFV DP expected to be associated with HIV prevention following administration of F/TDF 200/300 mg based on data from the iPrEX study (40 fmol/10^6 cells).

TFV-DP from TDF

The median predicted half-life of TFV-DP (~106 hours) following steady-state administration of TDF 300 mg was similar to the observed value (~132 hours, N 6 ; {Hawkins 2005}).
Two subjects were excluded from the analysis as they had insufficient data to reliably estimate the TFV-DP half-life. To account for the lower variability observed in the Phase 1 dataset, observed variability from the Phase 3 study with F/TDF (GS-US-311-1089) was used to simulate concentration values for the 5th and 95th percentiles, resulting in a conservative estimate of TFV-DP concentrations for the 5th percentile. Based on the median simulated TFV-DP concentration over time shown in Appendix Figure 2, participants (50th percentile and above) are expected to have TFV-DP concentrations ≥ 40 fmol/10^6 cells approximately 10 days after cessation of F/TDF 200/300 mg taken once daily.

Appendix Figure 2. Observed and Predicted PBMC-associated TFV-DP Concentrations with F/TDF 200/300 mg



Green dots: Observed PBMC associated TFV DP concentrations after the last dose of a stable HIV ARV regimen containing TDF 300 mg once daily from {Hawkins 2005}.
Solid and dotted black lines: Simulated median and 5th and 95th percentiles of TFV DP concentrations
Horizontal dotted black line: Concentration of TFV DP expected to be associated with HIV prevention following administration of F/TDF 200/300 mg based on data from the iPrEX study.

Summary

These analyses demonstrate that PBMC-associated concentrations of TFV-DP are anticipated to be at or above the threshold associated with HIV prevention in participants (50^{th} percentile and above) approximately 16 days and 10 days after cessation of multiple-dose F/TAF or F/TDF, respectively. As such, on-treatment HIV infections will be defined in GS-US-412-2055 as HIV infections diagnosed after first dose date through the last dose date +16 days for F/TAF or + 10 days for F/TDF.

Appendix 8. Predicted HIV Incidence Rate from Rectal Gonorrhea Rates

The predicted HIV-1 incidence rate, in the absence of PrEP, will be estimated using data from a linear regression model characterizing the expected HIV incidence rate as a function of anal/rectal gonorrhea incidence rate (as an indicator of engaging in sexual risk behavior putting subject at risk of acquiring HIV). This model is constructed based on incidence rates for HIV and rectal gonorrhea in 8 studies with MSM not using PrEP {Mullick 2019}. The studies and rates considered for constructing the model are listed in Appendix Table 7.

Appendix Table 7. Incidence of Rectal Gonorrhea Infection and HIV Infection in HIV-uninfected MSM not using PrEP

Source Publication	Rectal Gonorrhea Incidence (per 100 PY)	HIV Incidence (per 100 PY)	Study Location
Morris SR, CID 2006 (EXPLORE)	3.5	2.5	United States
Jin F, JAIDS 2010	2.3	0.9	Australia
Sanders 2014*	9.3	35.2	Kenya
Molina JM, NEJM 2015 (IPERGAY)	15.5	6.6	France, Canada
Castillo R, JAIDS 2015	10.1	3.6	Peru
Kelley CF, AIDS 2015	6.2	3.8	United States
McGowan I, PLOS One 2016	16.1	6.4	United States
McCormack S, Lancet 2016 (PROUD)	33.1	9.0	United Kingdom
Girometti N, Sex Transm Infect 2017	33.0	8.3	United Kingdom

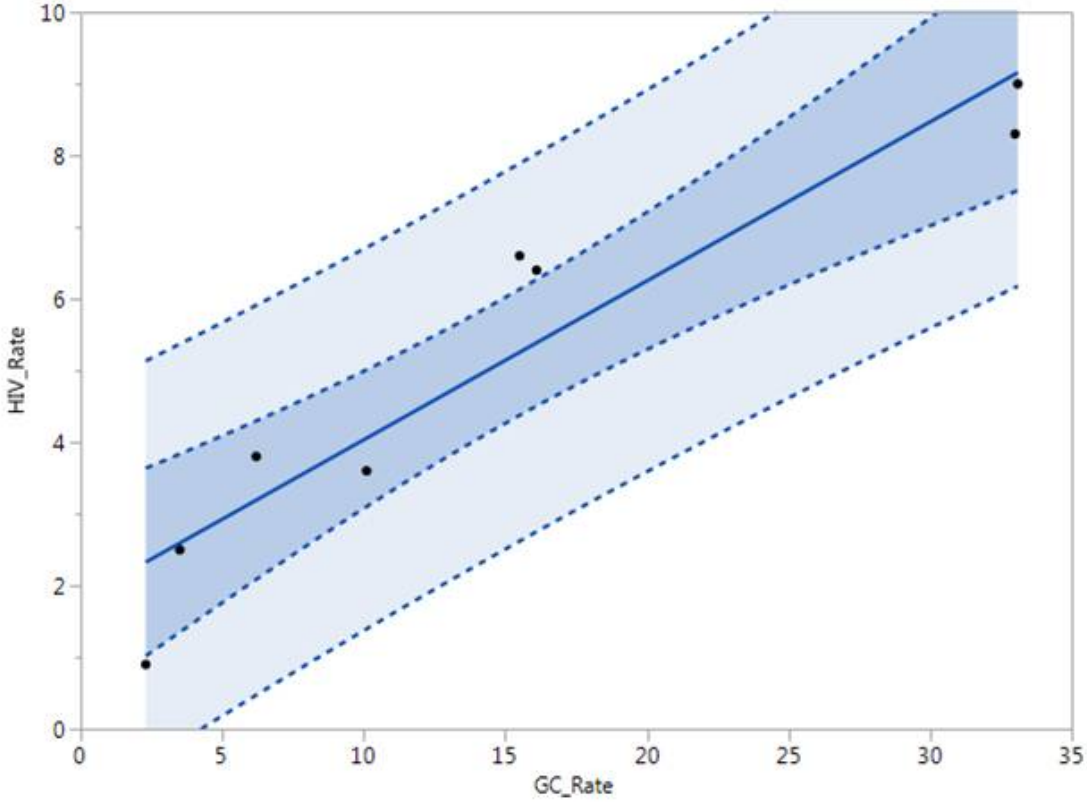
* Sanders data excluded from the model
{Mullick 2019}

Based on these data (excluding the Sanders 2014 rates) the constructed regression model is characterized by

$$\hat{y} \quad 1.8168 + 0.2218 \times x$$

where $\hat{y}$ is the predicted HIV-1 incidence rate (events/100PY) in the absence of HIV prophylaxis and x is the rectal gonorrhea incidence rate (events/100PY).

Appendix Figure 3. Graphical Presentation of the Regression Analysis from Data Points in 8 Studies



To assess if treatment with F/TAF (or F/TDF) is superior to the historical placebo with respect to the HIV-1 incidence rate, the following steps will be done:

1) Construct a 2-sided 95% prediction band around the regression line for the predicted HIV-1 incidence rate in the absence of HIV prophylaxis given the observed rectal gonorrhea incidence rate for study participants receiving F/TAF. This 95% prediction interval is characterized below:

$$\hat{y} \pm t_{n\ 2} \times s_y \sqrt{1 + \frac{1}{n} + \frac{(x\ \ \bar{x})^2}{(n\ \ 1)s_x^2}}$$

where n is the total number of studies in the meta-analysis, s_y is the standard deviation of the regression model residuals, s_x is the standard deviation anal/rectal gonorrhea incidence rates, $\bar{x}$ is the average anal/rectal gonorrhea incidence rate, and $t_{n\ 2}$ is the quantile for the 2-sided 95% t distribution with ($n\ \ 2$) degrees of freedom.

2) Construct a 2-sided 95% confidence interval for the observed HIV-1 incidence rate for study participants receiving F/TAF (or F/TDF). The 95% CI for the incidence rate is calculated using the following formula:

$$L_l = \frac{\chi^2_{2Y,\alpha/2}}{2D}$$

$$L_u = \frac{\chi^2_{2(Y+1),1-\alpha/2}}{2D}$$

where Y is the observed number of events, L_l and L_u are lower and upper confidence limits for Y respectively, D is the total follow-up duration, and $\chi^2_{v,\alpha}$ is the chi-square quantile for upper tail probability on v degrees of freedom (Ulm, 1990).

3) If $L_u = \min\left(L_u, \hat{y} - t_{n\ 2} \times s_y \sqrt{1 + \frac{1}{n} + \frac{(x-\bar{x})^2}{(n-1)s_x^2}}\right)$ then declare F/TAF (or F/TDF) superior to the historical placebo HIV-1 infection rate.

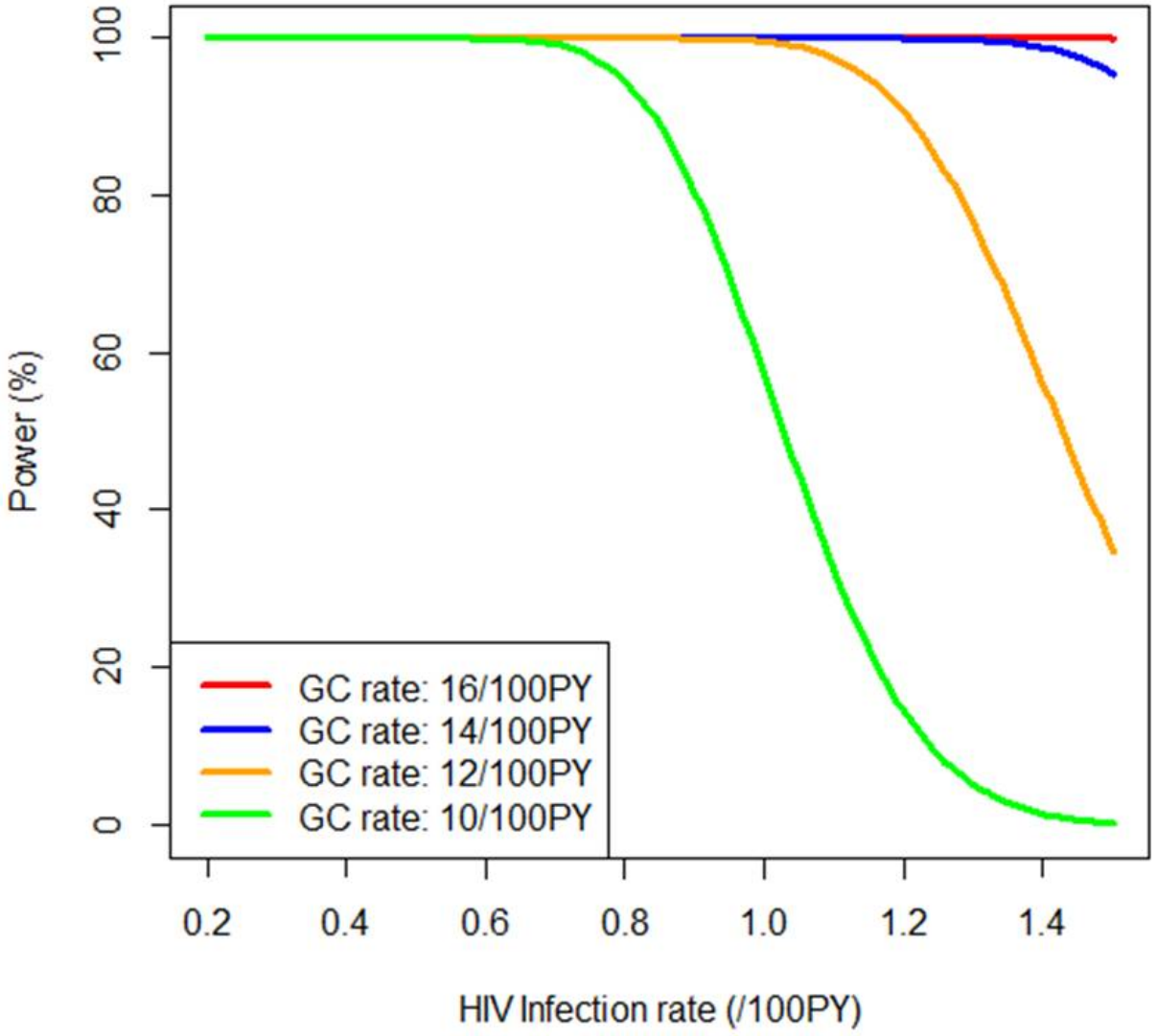
Appendix Table 8. Predicted HIV Incidence[a] Using Rectal Gonorrhea Incidence as the Determinant

Rectal Gonorrhea incidence (per 100 PY)	Predicted HIV Incidence Including 95% Prediction Interval (per 100 PY)
15	5.1 (2.51, 7.78)
20	6.3 (3.59, 8.91)
21	6.5 (3.80, 9.15)
22	6.7 (4.01, 9.38)
23	6.9 (4.21, 9.62)
24	7.1 (4.41, 9.86)
25	7.4 (4.62, 10.11)
30	8.5 (5.59, 11.34)
35	9.6 (6.63, 12.63)

a. Predictive model based on HIV and rectal gonorrhea regression analysis from 8 studies

Appendix Figure 4 below gives the power under different rectal gonorrhea rates and HIV infection rates. The power is calculated using the closed form power formula for the Poisson distribution, ie. not based on simulations.

Appendix Figure 4. Power for Superiority Test against Historical Placebo



Assuming 4250 PY follow up per arm (based on estimated follow up time by the time of the primary analysis).

Appendix 9 Assessment of Adherence and Efficacy Based on Dried Blood Spot Concentration

DBS 1.1 Background

Drug exposure level has been identified as the key factor in optimizing efficacy of HIV-1 PrEP. Although drug exposure level is related to multiple factors, adherence to drug (consistent drug administration) is the most important factor.

Two substudies will be conducted:

1) Cohort substudy to estimate the overall rate of adherence

2) Case-Control substudy to assess the association of adherence with efficacy in the GS-US-412-2055 study

The GS-US-412-2055 study is a randomized double-blind comparison of the safety and efficacy of F/TAF versus F/TDF administered once daily (QD) for at least 96 weeks in HIV-1 negative adults to show noninferiority of F/TAF to F/TDF with respect to prevention of HIV-1 infection. The study is being conducted in 94 sites across 11 countries in both North America and Europe. Enrollment for the GS-US-412-2055 study began in September 2016 and ended in June 2017. The primary endpoint will be assessed when all subjects have a minimum follow-up of 48 weeks and at least 50% of the subjects have 96 weeks of follow-up after randomization or permanently discontinued from the study.

Cards with dried blood samples (DBS) should be placed in a freezer within 1 day after blood draw and should be stored frozen for optimal stability. Samples put in a freezer later than one day after blood has been drawn or those with missing date for placement in the freezer will not be considered for these substudies and will not be sent to the analytical laboratory.

DBS 1.2 Exposure and Adherence

For these substudies, exposure is defined as tenofovir diphosphate (TFV-DP) concentration inside the red blood cells for each study drug group (F/TAF and F/TDF) as assessed by the dried blood spot (DBS concentration). Concentrations of TFV-DP in DBS assessments reflect cumulative exposure to study drug prior to the sampling time, and are not reflective of only the most recent daily dosing. Thus, as DBS concentration reflects long term exposure to study drug, it serves as an objective measure of overall or long-term adherence to study drug which is less affected by potential variability in daily drug administration (ie, missing a dose or doses, varying the time of day of drug administration).

TFV-DP concentrations are continuous measures and have been reported in units of femtomoles per punch (fmol/punch) or femtomoles per million viably cryopreserved peripheral blood mononuclear cells (f/M vPBMC). Previous work on DBS concentrations with F/TDF have been validated based on 3 mm punched disks.

Previous analyses {Anderson 2012a} of data from directly observed therapy (DOT) study (STRAND) in healthy volunteers along with the data from the iPrEX study have shown that F/TDF PrEP efficacy is associated with TFV-DP and that optimal efficacy may be achieved with concentrations consistent with ≥4 doses/week (see Appendix Table 9).

Appendix Table 9. TFV-DP Concentrations after DOT Dosing of F/TDF (STRAND Study) and Associated Risk Reduction and Proportion of Subjects Attaining TFV-DP EC90 in the iPrEx Study

	STRAND Study			iPrEX	
Regimen	**Concentration (fmol/M vPBMC)**			**HIV-1 Acquisition Risk Reduction**	**Subjects Attaining TFV-DP EC_{90}**
(Doses / Week)	**25 Percentile**	**Median**	**75 Percentile**		
2	6	11	13	76%	14%
4	25	32	39	96%	90%
7	31	42	47	99%	100%

Source: Emtricitabine tenofovir concentrations and pre exposure prophylaxis efficacy in men who have sex with men {Anderson 2012a}

A 72 week open-label cohort study {Grant 2014} of men and transgender women who have sex with men in previously enrolled PrEP trials (ATN 082, iPrEx, and US Safety Study) reported consistent results, Appendix Table 10**.**

Appendix Table 10. Estimated Dose and F/TDF PrEP Protection Associated with DBS Concentration

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

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

A more recent pharmacokinetic study of TFV-DP in DBS using DOT dosing of F/TDF (at daily dosing of 33%, 67%, or 100%) {Anderson 2018} has also shown consistent results. The modeling of data from this study has shown that the fitted (estimated) median (25 and 75 percentiles) TFV-DP DBS concentrations in men, were 375 (316, 444), 774 (653, 917) and 1389 (1173, 1646) fmol/punch for 2, 4 and 7 doses per week respectively {Anderson 2018}.

Considering that F/TAF delivers a lower dose of tenofovir and that using a 3 mm punch disk to quantify the TFV-DP levels in RBC are approximately 1/8th the values established for F/TDF, two 7 mm punched disks (an increase of 10.89 folds in total sample disk area) are used to quantify TFV-DP DBS concentration for participants who receive F/TAF.

A separate cross-over pharmacokinetic study of TFV-DP in DBS based on DOT dosing of F/TAF (at daily dosing of 33%, 67%, or 100%) is currently ongoing. Available preliminary data from this ongoing study {Yager 2019} (CROI abstract and presentation), and the previous F/TDF DOT study {Anderson 2018}, are used to develop the adherence bands for F/TAF based on DBS concentration. The observed 25th percentile, median and 75 percentiles from these sources are presented in Appendix Table 11.

Appendix Table 11. Reported Estimates of DBS Concentrations at Different DOT Dose Levels

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

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

As expected (relative to TDF dose in F/TDF and DBS disk size), a shift up in the distribution of reported TFV-DP concentrations for F/TAF, compared to F/TDF, in Appendix Table 11 is observed; ~30% based the Week 12 data (Period 1 of the cross over study) and ~35% based the Weeks 12 and 24 data (Period 1and 2 of the cross over study) included in the analysis of the abstract and presentation respectively. The cutoffs for F/TAF adherence levels can be estimated by adjusting the established DBS concentration for F/TDF adherence levels associated with HIV protection (or risk of acquiring infection) reported by {Grant 2014}, see Appendix Table 10. The proposed cutoffs, by either using 30% increase based on Period 1 results (free of any potential impact of cross-over design) or assuming dose proportionality and relying on Q1 for the 33% and 67% dosing levels, are presented in Appendix Table 12.

Appendix Table 12. Adherence Level Definitions Based on DBS Concentration

	Adherence Level (Daily Tablets/Week)		
	Low (<2)	**Medium (2-3)**	**High (≥4)**
F/TDF (fmol/Punch)	< 350	350 to < 700	≥ 700
F/TAF (fmol/Punches)	< 450	450 to < 900	≥ 900

These cutoffs for F/TAF may change or additional sensitivity analysis may be conducted if the updated data from the ongoing DOT study of F/TAF or the analysis of adherence bands associated with TFV-DP concentrations (fitted results) are completed and are available to Gilead.

DBS 1.3 The Cohort Substudy

DBS 1.3.1 Study Design

In order to estimate the rate of adherence based on the DBS concentration, a cohort of approximately 10% of the subjects who were randomized in Study GS-US-412-2055 were randomly pre-selected. The subjects were selected early during study conduct (December 2016) based on the planned subject number ranges for the study (starting with 2000). The selection for the Cohort substudy, randomly selected 1 out of every 10 subject numbers expected to be used for enrollment (Section 1.2, Pharmacokinetics).

DBS 1.3.2. Objective

The primary objective of the cohort substudy is to characterize the overall adherence for each treatment group.

DBS 1.3.3. Implementation

In order to lower the burden on the laboratory analyzing DBS cards, subsets of DBS cards will be sent to the analytic laboratory. This will be done by sending subsets of Week 4 samples first. Week 12 subsets of samples will be sent when Week 4 samples have been analyzed and etc. as subjects complete the study visits. For example, as of February 2018, all subjects had completed their Week 24 visit and we could potentially process Weeks 4, 12 and 24 samples for the randomly selected subjects. The size of the batch will depend on the logistics at the analytic laboratory. Further details are provided in the charter for DBS sample analysis project plan conducted at Colorado Antiviral Pharmacology Laboratory (University of Colorado).

The unblinded statistician supporting the external DMC will execute a SAS program to select, for each batch, the accession numbers in the cohort substudy and will:

1) Provide the accession number of the selected DBS cards to Covance (central warehousing lab for DBS cards) for transfer to the analytic lab (University of Colorado). Covance will receive the following information: Investigator ID, Subject ID, Lab Date, Accession Number and Container Number (of sample storage at Covance).
2) Provide the treatment code for each accession number to the analytic lab as measuring DBS concentration for F/TAF requires a bigger punch-hole on the DBS card compared to F/TDF. The analytic lab will receive the following information: Investigator ID, Subject ID, Lab Date, Treatment group and Accession Number.

DBS 1.3.4. Statistical Analysis

Summary tables, similar to those for the main study, will characterize the Cohort substudy for enrollment by country and investigator, demographics and baseline characteristics, baseline HIV risk characteristics, and subject disposition.

Descriptive statistics (n, mean, standard deviation, median, quartiles, minimum and maximum) for DBS TFV-DP concentration levels will be provided by treatment group and visit.

Median (Q1, Q3) of DBS concentration across visit time (horizontal axis) overlaid by horizontal lines corresponding to adherence thresholds for each treatment group, will be generated by treatment group.

DBS 1.4. Case-Control Substudy

DBS 1.4.1. Study Design

Matched case control study nested in a clinical trial

DBS 1.4.2. Objective

The primary objective of this case control evaluation is to assess the effect of adherence on HIV-1 PrEP efficacy (prevention of HIV-1 infection).

DBS 1.4.3. Definition of Case

All study participants who become HIV-1 infected after having been randomized to study treatment in the GS-US-412-2055 trial are the cases for this case-control substudy. The HIV-1 infection definition can be found in the SAP (Section 6.2.2).

DBS 1.4.4. Selection of Controls

A matching subset of the HIV-1 uninfected subjects will be selected as controls for this case-control substudy.

DBS 1.4.5. Matching

In this matched case-control substudy, control subjects will be matched to cases on a 5:1 ratio based on the following criterion order

1) Treatment group

2) Time of HIV-1 diagnosis, where time is defined as the visit that an HIV-1 case was first considered to be HIV-1 positive based on laboratory data; as subject visit varies, a visit window will be applied to identify the visit that is considered to be the HIV-1 infection visit. The visit windows for HIV-1 infection will be contiguous and centered at the mid-point of scheduled study visits (nominal day) as defined in Table 3-1 of the main SAP and the control subjects are selected based on the same visit windows as specified in Appendix Table 13.

Appendix Table 13. Analysis Windows for Selection of Control Subjects

Visit ID	Nominal Day	Lower Limit	Upper Limit
Week 4	28	1	56
Week 12	84	57	126
Week K (K is every 12 weeks after Week 12 visit)	K*7	(K-6)*7+1	(K+6)*7

For both cases and controls, the concentrations from DBS at the time of HIV-1 diagnosis as well as at all previous post-baseline visits will also be measured to provide a clearer assessment of long term drug adherence.

3) Risk behavior as indexed by diagnosis of either rectal gonorrhea or rectal chlamydia (rectal STI [rSTI] collectively). Cases who are diagnosed with post-Day 1 rSTI prior to HIV-1 infection are matched to controls who are diagnosed with rSTI prior to HIV-1 infection time of the case subject (ie, a case subject who was diagnosed with HIV-1 at Week 48 and was diagnosed with rSTI prior to Week 48 is matched to control subjects who were diagnosed with rSTI between Day 1 and Week 48 in the study).

4) Location: As the number of subjects from each site varies, the matching location will be selected based on widening the geographic area in the following order to achieve the total number of controls

   a) Investigational site (enrolled by the same investigator)

   b) City (based on address)

   c) Metropolitan area (based on address cities, grouping cities in close proximity such as Bronx and New York).

   d) For US: i) State then ii) one of four US Regions (Northeast, Midwest, South or West as specified in Appendix 3.)

      For Non-US: i) Country then Region; where European region includes UK and countries of Western Europe and for Canada, Region Country (Canada and the US are not pooled into one region due to differences in structure of social medicine).

Control subjects will be selected randomly if the available number of control subjects meeting the above criteria exceeds 5 in a site or a geographic area. For example, if there are 2 matching controls at the same investigational site and 10 additional in the same city (from other investigational sites), then the first two will be selected from the site and the next 3 will be picked randomly among the other 10 available in the same city.

Some subjects may move, due to personal reasons, from one city to another city, within a continent, while continuing in the study, the location criteria will be implemented based on the subject's current investigator and/or city (as tracked by the IxRS system).

Due to logistic issues at Covance (central warehousing lab for DBS cards), uninfected subjects who have intercontinental site transfers (North America ↔ Europe) during the study will not be selected as controls. As of September 2018, there were only 13 such subjects in the GS-US-412-2055 study.

A subject who meets the above criteria but is diagnosed with HIV-1 at a later date compared to the case subject (later than the upper limit of the window) is allowed to be selected as a control subject (ie, a subject who is HIV-1 infected at Week 60 may serve as a control for a Week 12 infection if other matching criteria are met).

DBS 1.4.6. Implementation

In order to lower the burden on the laboratory analyzing DBS cards, selection of matches may be done in batches as subjects complete study visits (upper bound of visit window as specified above). Control subjects, who have available DBS cards, will be identified from the pool of HIV-1 negative subjects matching to each case subject. For example, when all subjects complete the Week 24 visit (plus 6 weeks) then the matching controls could be selected for all infections on or prior to Week 24. A SAS program will be utilized for the random selection of controls based on DBS accession numbers. A uniform random number will be assigned to each DBS accession number. The rank of the random numbers will be used for random selection of controls. Thus, the samples from the first 5 ranked subjects will be selected.

A date stamped dataset for each infected subject (case) with all the details on available control subjects will be generated and archived for future reference.

As the first matching criterion is treatment group, the unblinded statistician supporting the external DMC will execute the SAS program to:

1) Provide the accession number of the selected DBS cards to Covance (central warehousing lab for DBS cards) for transfer to the analytic lab (University of Colorado). Covance will receive the following information: Investigator ID, Subject ID, Lab Date, Accession Number, and Container Number (of sample storage at Covance).

2) Provide the treatment code for each accession number to the analytic lab as measuring DBS concentration for F/TAF requires a bigger punch-hole on the DBS card compared to F/TDF. The analytic lab will receive the following information: Investigator ID, Subject ID, Lab Date, Treatment group and Accession Number.

The DBS concentration data for each batch will be transferred to the unblinded statistician. The unblinded statistician will manage the data batches to create datasets for DBS concentrations and identify HIV infected subjects (cases) and their matched controls, including Subject ID, investigator ID, treatment group, strata ID (to indicate a case and matched controls), sample date,

sample day (relative to Day 1), concentration and other relevant data. This dataset will be transferred to Gilead after study unblinding for the primary analysis. The raw Excel files (and their PDF versions) for each batch will be sent to Gilead from both the unblinded statistician and the analytical lab (University of Colorado) for long term archiving.

This process protects the integrity of the study as it insures that the staffs at Gilead and Covance remain blinded to the study drug assignment at the subject level.

DBS 1.4.7. Statistical Analysis

Summary tables, similar to those for the main study, will characterize the cases' and controls' demographics and baseline characteristics, baseline HIV risk characteristics and subject disposition by treatment group.

Graphical and/or tabular descriptive statistics (n, mean, standard deviation, median, quartiles, minimum and maximum) for DBS drug concentration levels for both cases and controls in each treatment group will be provided. Conditional logistic regression model will be used to estimate the odds ratio (and its 95% confidence interval) assessing the association between infection status and the adherence levels based on DBS concentration at HIV diagnosis for cases and controls. The 3 level adherence (Appendix Table 12) will be dichotomized to estimate two odds ratios:

1) the odds of HIV infection when adherence is low compared to when adherence is not low

2) the odds of HIV infection when adherence is high compared to when adherence is not high

The primary analysis will be within each treatment group and will include DBS drug concentration levels, at the time of infection as the primary predictor. If a control subject has DBS collected at more than one visit within a window, then the record with DBS collection study day closest to the diagnosis study day of the case subject will be selected and if they are equally apart from the diagnosis study day of the case subject (one before and one after) then the one after the study day of the case subject will be selected.

DBS cards at the time of diagnosis may not have been collected for infected subjects or the sample may not meet specifications and be rejected by the analytical laboratory. In general, missing DBS concentration at the time of HIV diagnosis will be imputed by considering:

1) the last known TFV-DP concentration (C) prior to diagnosis

2) days between the last dose date and HIV diagnosis (HIV Dx date last dose date) where any negative days (last dose is after HIV Dx) are set to 0

3) days between the last TFV-DP concentration (C) prior to diagnosis and HIV diagnosis (HIV Dx date last DBS date)

4) the decay rate, k, of TFV-DP concentration in RBC calculated based on half-life, $t_{1/2}$, of each treatment group, where k $0.693/t_{1/2}$.

The imputed concentration, C_i $C \times e^{k \times t}$, where t is the min of 2) and 3) above.

TFV-DP has shown the median (range) half-life of 17 (14 to 23) days for F/TDF in previous DOT studies of F/TDF {Anderson 2018} and median (IQR) 20 days (18, 21) for F/TAF (preliminary data from Yager 2019 CROI presentation).

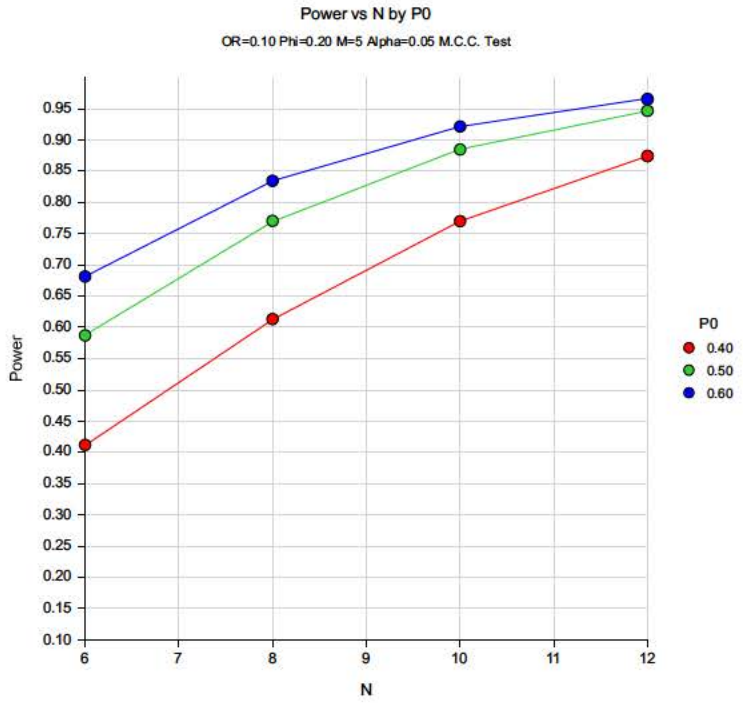
A sensitivity analysis will be conducted by setting the adherence level to "Low", for subjects suspected to have acquired HIV prior to first dose date of study drug. These are defined as subjects for whom HIV infection prior to first dose date of study drug cannot be excluded as the subjects did not have a Covance HIV antibody or HIV-1 RNA test analyzed between first dose date (inclusive) and prior to the date of diagnosis of HIV infection).

Stratified Wilcoxon test (stratified based on matching criteria) will test the difference between distribution of DBS concentrations (continuous measure) observed in cases and controls. The two-sided p-value from the stratified Wilcoxon test will be reported.

DBS 1.5. Power and Sample Size

In a matched case-control study, where the correlation coefficient for exposure between matched case and control subjects is 0.2, a matching sample of 5 control subjects for each of the10 cases within a treatment group (Total, Cases+Controls, Number of subjects 60) provides 88% power to detect an odds ratio of 0.10 versus the alternative of equal odds using a Chi-Square test at a 0.05 significance level if the probability of exposure among sampled control subject patients is 0.5. The power increases to 92% if the probability of exposure among sampled control subjects is increased to 0.6 (source: PASS 14).

Appendix Figure 5. Matched Case-Control Power vs. Number of Cases (N) in Each Treatment Group for 5 Matched Controls



Matched case-control power vs number of cases (N) in each treatment group for 5 matched controls with probability of exposure (P0) 0.4, 0.5 and 0.6 and correlation (phi) between matched individuals 0.2 to test OR 0.1 at 0.05 significance level.

Appendix 10. Adverse Events of Interest

	Selected PTs
Proximal Renal Tubulopathy	• Fanconi syndrome • Fanconi syndrome acquired • Renal tubular disorder • Renal tubular dysfunction • Renal tubular injury
Diarrhea	Diarrhea
Nausea	Nausea
Abdominal Pain	Abdominal Pain

Appendix 11. Selected Medical History

Subjects with selected medical history of Diabetes Mellitus, Hypertension, Cardiovascular Disease, and Hyperlipidemia will be identified. A subject who had medical history of one of these diseases is a subject who experience at least one of the following events:

- At least 1 medical history record with MedDRA PT (mh.MDRPT) in the following selected PT listing for the corresponding disease with start date on or prior to the DB phase first dose date.
- At least 1 AE record with MedDRA PT (ae.MDRPT) in the following selected PT listing for the corresponding disease with start date on or prior to the DB phase first dose date.
- At least 1 concomitant medications record with medication class and indication in the following selected listing for the corresponding disease with start date on or prior to the DB phase first dose date.

If the start date is incomplete but the month and year (or year alone) of the start date is the same as or before the month and year (or year alone) of the first dosing date of randomized study drug, the event will be included. If the start date is completely missing, the event will be included.

Four variables (ie, DIABETES, HTENSION, CARDDIS, and HLIPDEM) will be added to raw Medical History and Adverse Events datasets. A medical history or an AE record will be flagged for a disease of interest if its MedDRA PT included in the prespecified PT list for the corresponding disease of interest, which include all PTs from the narrow or broad search of the following SMQs under MedDRA 19.1 provided by Gilead DSPH and reviewed by Gilead medical monitors.

Disease of Interest	SMQ Source
Diabetes Mellitus (DIABETES)	Hyperglycaemia/new onset diabetes mellitus (SMQ) Narrow Scope Term
Hyperlipidemia (HLIPDEM)	Dyslipidaemia (SMQ)
Hypertension (HTENSION)	Hypertension (SMQ)
Cardiovascular disease (CARDDIS)	Ischaemic central nervous system vascular conditions (SMQ) Narrow Scope Term
	Myocardial infarction (SMQ) Narrow Scope Term
	Other ischaemic heart disease (SMQ) Narrow Scope Term

Similarly, two variables (ie, DRUGF and DRUGTYP) will be added to raw Concomitant Medication dataset. A concomitant medication record will be flagged for a disease of interest if its medication class and indication included in the following listing for the corresponding disease of interest.

The selected combination of medication class and indication are listed as follows, which was reviewed by Gilead medical monitors.

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
Hypertension (HTENSION)			
1	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM		LISINOPRIL
2	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ANTI HYPERTENSIVE	LOSARTAN
3	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPENTENSION	RAMIPRIL
4	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	CAPTOPRIL
5	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	ENALAPRIL
6	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	HYDROCHLOROTHIAZIDE W/OLMESARTAN
7	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	OLMESARTAN MEDOXOMIL
8	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	RAMIPRIL
9	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	SALUTEC
10	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION	VALSARTAN
11	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION STAGE I	CAPTOPRIL
12	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION STAGE 1	CANDESARTAN
13	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	BENIGN ESSENTIAL HYPERTENSION	LISINOPRIL
14	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	BENIGN ESSENTIAL HYPERTENSION	LOSARTAN
15	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL (PRIMARY) HYPERTESION	ZESTORETIC
16	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	COROVAL B
17	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	ENALAPRIL MALEATE
18	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	LISINOPRIL
19	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	LOSARTAN
20	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	TRIBENZOR
21	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION	ZESTORETIC
22	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ESSENTIAL PRIMARY HYPERTENSION	IRBESARTAN
23	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	COVERAM
24	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	ENALAPRIL
25	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	IRBESARTAN

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
26	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	LISINOPRIL
27	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	LOSARTAN
28	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	LOSARTAN POTASSIUM
29	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE	RAMIPRIL
30	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HIGH BOLD PRESSURE	LOSARTAN
31	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HISTORY OF MYOCARDITIS	RAMIPRIL
32	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HTN	ZESTORETIC
33	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERRTENSION	ZESTORETIC
34	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTEENSION	LISINOPRIL
35	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	AMLODIPINE W/HYDROCHLOROTHIAZIDE/ VALSARTAN
36	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	AMLODIPINE W/VALSARTAN
37	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	BENAZEPRIL
38	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	BENAZEPRIL HYDROCHLORIDE
39	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	BENICAR HCT
40	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	BI PREDONIUM
41	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	CANDESARTAN
42	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	CANDESARTAN CILEXETIL
43	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	CAPTOPRIL
44	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	CO DIOVAN
45	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	COROVAL B
46	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	DIOVAN AMLO
47	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	DIOVAN TRIPLE
48	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	EDARBYCLOR
49	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	ENALAPRIL
50	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	ENALAPRIL MALEATE

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
51	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	FOSINOPRIL
52	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	HYDROCHLOROTHIAZIDE W/LOSARTAN
53	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	HYZAAR
54	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	IRBESARTAN
55	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	KARVEA HCT
56	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	LISINOPRIL
57	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	LOSARTAN
58	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	LOSARTAN POTASSIUM
59	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	NAPRIX A
60	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	OLMESARTAN MEDOXOMIL
61	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	PERINDOPRIL ERBUMINE
62	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	PRITORPLUS
63	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	QUINAPRIL
64	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	RAMIPRIL
65	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	SALUTEC
66	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	TELMISARTAN
67	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	TRIBENZOR
68	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	VALSARTAN
69	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	VASERETIC
70	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION	ZESTORETIC
71	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION ESSENTIAL	CANDESARTAN CILEXETIL
72	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION ESSENTIAL	DIOVAN TRIPLE
73	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION, BENIGN	LISINOPRIL
74	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION, BILATERAL LOWER LEG SWELLING	LISINOPRIL
75	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION, ESSENTIAL	ZESTORETIC
76	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSION, WORSENING HYPERTENSION	LISINOPRIL

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
77	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSIONPROPHYLAXIS	RAMIPRIL
78	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSIVE	RAMIPRIL
79	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENSIVE CRISIS	CAPTOPRIL
80	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTENTION	LISINOPRIL
81	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTONIA	RAMIPRIL
82	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPOKALEMIA	LOSARTAN POTASSIUM
83	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	POOR CONTROL OF BLOOD PRESSURE	LISINOPRIL
84	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	PREVENTATIVE FOLLOWING ACUTE MYCARDIAL INFARCTION	PERINDOPRIL
85	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	PRIMARY ESSENTIAL HYPERTENSION	ENALAPRIL MALEATE
86	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	PROTEINURIA	BENAZEPRIL
87	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	PROTEINURIA	ENALAPRIL
88	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	PROTEINURIA	LISINOPRIL
89	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	WORSENING HYPERTENSION	BENAZEPRIL
90	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	WORSENING HYPERTENSION	PERINDOPRIL
91	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	WORSENING HYPERTENSION	PRETERAX ARGININE
92	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	WORSENING OF HYPERTENSION	LISINOPRIL
93	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	WORSENING OF HYPERTENSION	RAMIPRIL
94	ANTIHYPERTENSIVES	BENIGN HIGH BLOOD PRESSURE	DOXAZOSIN
95	ANTIHYPERTENSIVES	EXACERBATION OF HYPERTENSION	CLONIDINE
96	ANTIHYPERTENSIVES	HEADACHE	HYDRALAZINE
97	ANTIHYPERTENSIVES	HIGH BLOOD PRESSURE	CLONIDINE HYDROCHLORIDE
98	ANTIHYPERTENSIVES	HIGH BLOOD PRESSURE	RILMENIDINE
99	ANTIHYPERTENSIVES	HYPERTENSION	CLONIDINE
100	ANTIHYPERTENSIVES	HYPERTENSION	CLONIDINE HYDROCHLORIDE
101	ANTIHYPERTENSIVES	HYPERTENSION	DOXAZOSIN
102	ANTIHYPERTENSIVES	HYPERTENSION	DOXAZOSIN MESILATE
103	ANTIHYPERTENSIVES	HYPERTENSION	HYDRALAZINE
104	ANTIHYPERTENSIVES	HYPERTENSION	HYDRALAZINE HYDROCHLORIDE
105	ANTIHYPERTENSIVES	HYPERTENSION	METHYLDOPA
106	ANTIHYPERTENSIVES	HYPERTENSION	TADALAFIL

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
107	ANTIHYPERTENSIVES	PULMONARY HYPERTENSION	TADALAFIL
108	ANTIHYPERTENSIVES	VASODILATION STENT PROCEDURE	HYDRALAZINE
109	ANTIHYPERTENSIVES	WORSENING HYPERTENSION	HYDRALAZINE HYDROCHLORIDE
110	BETA BLOCKING AGENTS	ARTERIAL HYPERTENSION	ATENOLOL
111	BETA BLOCKING AGENTS	ARTERIAL HYPERTENSION	METOPROLOL SUCCINATE
112	BETA BLOCKING AGENTS	ARTERIAL HYPERTENSION / ICHEMIC HEART DISEASE	BISOPROLOL
113	BETA BLOCKING AGENTS	ESSENTIAL HYPERTENSION	METOPROLOL
114	BETA BLOCKING AGENTS	HEART FAILURE AND HYPERTENSION	CARVEDILOL
115	BETA BLOCKING AGENTS	HEART HEALTH	ATENOLOL
116	BETA BLOCKING AGENTS	HIGH BLOOD PRESSURE	ATENOLOL
117	BETA BLOCKING AGENTS	HIGH BLOOD PRESSURE	BISOPROLOL W/HYDROCHLOROTHIAZIDE
118	BETA BLOCKING AGENTS	HIGH BLOOD PRESSURE	METOPROLOL
119	BETA BLOCKING AGENTS	HISTORY OF MYOCARDITIS	BISOPROLOL
120	BETA BLOCKING AGENTS	HYPERTENSION	ATENOLOL
121	BETA BLOCKING AGENTS	HYPERTENSION	BISOPROLOL FUMARATE
122	BETA BLOCKING AGENTS	HYPERTENSION	CARVEDILOL
123	BETA BLOCKING AGENTS	HYPERTENSION	LABETALOL
124	BETA BLOCKING AGENTS	HYPERTENSION	METOPROLOL
125	BETA BLOCKING AGENTS	HYPERTENSION	METOPROLOL SUCCINATE
126	BETA BLOCKING AGENTS	HYPERTENSION	METOPROLOL TARTRATE
127	BETA BLOCKING AGENTS	HYPERTENSION	NEBICARD V
128	BETA BLOCKING AGENTS	HYPERTENSION	NEBICARD H
129	BETA BLOCKING AGENTS	HYPERTENSION	NEBIVOLOL
130	BETA BLOCKING AGENTS	HYPERTENSION	NEBIVOLOL HYDROCHLORIDE
131	BETA BLOCKING AGENTS	HYPERTENSION	PROPRANOLOL
132	BETA BLOCKING AGENTS	HYPERTENSION	PROPRANOLOL HYDROCHLORIDE
133	BETA BLOCKING AGENTS	HYPERTENSION AND MIGRAINE	ATENOLOL
134	BETA BLOCKING AGENTS	HYPERTENSION ESSENTIAL	ATENOLOL
135	BETA BLOCKING AGENTS	HYPERTENTION	METOPROLOL SUCCINATE
136	BETA BLOCKING AGENTS	HYPETENSION	BISOPROLOL
137	BETA BLOCKING AGENTS	PAROXYSM OF SINUS TACHYCARDIA	PROPRANOLOL
138	BETA BLOCKING AGENTS	PRIMARY ESSENTIAL HYPERTENSION	CARVEDILOL
139	BETA BLOCKING AGENTS	RAPID HEART BEAT	METOPROLOL SUCCINATE
140	CALCIUM CHANNEL BLOCKERS	ANTIHYPERTENSIVE	AMLODIPINE
141	CALCIUM CHANNEL BLOCKERS	ARTERIAL HYPERTENSION	AMLODIPINE
142	CALCIUM CHANNEL BLOCKERS	ARTERIAL HYPERTENSION	VERAPAMIL
143	CALCIUM CHANNEL BLOCKERS	ATRIAL FIBRILLATION	DILTIAZEM
144	CALCIUM CHANNEL BLOCKERS	ELEVATED BLOOD PRESSURE	AMLODIPINE
145	CALCIUM CHANNEL BLOCKERS	ELEVATED BLOOD PRESSURE	AMLODIPINE BESILATE
146	CALCIUM CHANNEL BLOCKERS	ESSENTIAL HYPERTENSION	AMLODIPINE

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
147	CALCIUM CHANNEL BLOCKERS	ESSENTIAL HYPERTENSION	AMLODIPINE BESILATE
148	CALCIUM CHANNEL BLOCKERS	ESSENTIAL HYPERTENSION	FELODIPINE
149	CALCIUM CHANNEL BLOCKERS	ESSENTIAL PRIMARY HYPERTENSION	AMLODIPINE
150	CALCIUM CHANNEL BLOCKERS	HIGH BLOOD PRESSURE	AMLODIPINE
151	CALCIUM CHANNEL BLOCKERS	HTN	AMLODIPINE
152	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	AMLODIPINE
153	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	AMLODIPINE BESILATE
154	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	BARNIDIPINE HYDROCHLORIDE
155	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	DILTIAZEM
156	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	DILTIAZEM HYDROCHLORIDE
157	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	FELODIPINE
158	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	NIFEDIPINE
159	CALCIUM CHANNEL BLOCKERS	HYPERTENSION	VERAPAMIL
160	CALCIUM CHANNEL BLOCKERS	HYPERTENSION (ESSENTIAL/PRIMARY)	VERAPAMIL HYDROCHLORIDE
161	CALCIUM CHANNEL BLOCKERS	HYPERTENSION ESSENTIAL	FELODIPINE
162	CALCIUM CHANNEL BLOCKERS	HYPERTNESION	AMLODIPINE BESILATE
163	CALCIUM CHANNEL BLOCKERS	HYPTERTENSION	AMLODIPINE
164	CALCIUM CHANNEL BLOCKERS	PRESTUDY HYPERTENSION	AMLODIPINE
165	CALCIUM CHANNEL BLOCKERS	SECONDARY STROKE PREVENTION	AMLODIPINE
166	CALCIUM CHANNEL BLOCKERS	SICK SINUS SYNDROME	VERAPAMIL
167	CALCIUM CHANNEL BLOCKERS	WORSENING OF HYPERTENSION	AMLODIPINE
168	CARDIAC THERAPY	HYPERTENSION	UBIDECARENONE
169	DIURETICS	ARTERIAL HYPERTENSION	HYDROCHLOROTHIAZIDE
170	DIURETICS	BENIGN ESSENTIAL HYPERTENSION	HYDROCHLOROTHIAZIDE
171	DIURETICS	BORDERLINE HYPERTENSION	HYDROCHLOROTHIAZIDE
172	DIURETICS	DIURETIC	FUROSEMIDE
173	DIURETICS	ELEVATED BLOOD PRESSURE READING, WITHOUT DIAGNOSIS OF HYPERTENSION	HYDROCHLOROTHIAZIDE
174	DIURETICS	ESSENTIAL HYPERTENSION	FUROSEMIDE
175	DIURETICS	ESSENTIAL HYPERTENSION	HYDROCHLOROTHIAZIDE
176	DIURETICS	HIGH BLOOD PRESSURE	HYDROCHLOROTHIAZIDE
177	DIURETICS	HYPERTENSION	AMILORIDE
178	DIURETICS	HYPERTENSION	BUMETANIDE
179	DIURETICS	HYPERTENSION	CHLORTALIDONE
180	DIURETICS	HYPERTENSION	DYAZIDE
181	DIURETICS	HYPERTENSION	FUROSEMIDE
182	DIURETICS	HYPERTENSION	HYDROCHLOROTHIAZIDE
183	DIURETICS	HYPERTENSION	INDAPAMIDE
184	DIURETICS	HYPERTENSION	MODURETIC
185	DIURETICS	HYPERTENSION	SPIRONOLACTONE
186	DIURETICS	HYPERTENSION	TRIAMTERENE
187	DIURETICS	HYPERTENSION, BENIGN	HYDROCHLOROTHIAZIDE

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
188	DIURETICS	HYPERTENTION	HYDROCHLOROTHIAZIDE
189	DIURETICS	WORSENING HYPERTENSION	HYDROCHLOROTHIAZIDE
190	LIPID MODIFYING AGENTS	HIGH BLOOD PRESSURE	PRAVASTATIN
191	LIPID MODIFYING AGENTS	HIGH BLOOD PRESSURE	PRAVASTATIN SODIUM
Diabetes Mellitus (DIABETES)			
1	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	DIABETES MELLITUS TYPE II	LISINOPRIL
2	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	TYPE 2 DIABETES	LISINOPRIL
3	ANTIHYPERTENSIVES	UNCONTROLLED DIABETES MELLITUS 2	CLONIDINE HYDROCHLORIDE
4	ANTIHYPERTENSIVES	UNCONTROLLED DIABETES MELLITUS 2	HYDRALAZINE HYDROCHLORIDE
5	BETA BLOCKING AGENTS	TYPE 2 DIABETES	METOPROLOL TARTRATE
6	DRUGS USED IN DIABETES	BORDERLINE DIABETES	METFORMIN
7	DRUGS USED IN DIABETES	DIABETES	DULAGLUTIDE
8	DRUGS USED IN DIABETES	DIABETES	GLIBENCLAMIDE
9	DRUGS USED IN DIABETES	DIABETES	GLICLAZIDE
10	DRUGS USED IN DIABETES	DIABETES	GLIMEPIRIDE
11	DRUGS USED IN DIABETES	DIABETES	GLIPIZIDE
12	DRUGS USED IN DIABETES	DIABETES	HUMAN MIXTARD
13	DRUGS USED IN DIABETES	DIABETES	INSULIN
14	DRUGS USED IN DIABETES	DIABETES	INSULIN ASPART
15	DRUGS USED IN DIABETES	DIABETES	INSULIN DETEMIR
16	DRUGS USED IN DIABETES	DIABETES	INSULIN GLARGINE
17	DRUGS USED IN DIABETES	DIABETES	INSULIN HUMAN
18	DRUGS USED IN DIABETES	DIABETES	INSULIN LISPRO
19	DRUGS USED IN DIABETES	DIABETES	METAGLIP
20	DRUGS USED IN DIABETES	DIABETES	METFORMIN
21	DRUGS USED IN DIABETES	DIABETES	METFORMIN HYDROCHLORIDE
22	DRUGS USED IN DIABETES	DIABETES	PIOGLITAZONE
23	DRUGS USED IN DIABETES	DIABETES	PIOGLITAZONE HYDROCHLORIDE
24	DRUGS USED IN DIABETES	DIABETES	SITAGLIPTIN
25	DRUGS USED IN DIABETES	DIABETES TYPE I	INSULIN GLARGINE
26	DRUGS USED IN DIABETES	DIABETES TYPE I	INSULIN LISPRO
27	DRUGS USED IN DIABETES	DIABETES 2	GLICLAZIDE
28	DRUGS USED IN DIABETES	DIABETES II	METFORMIN
29	DRUGS USED IN DIABETES	DIABETES KETOACIDOSIS	INSULIN
30	DRUGS USED IN DIABETES	DIABETES MELL. TYPE 2	INSULIN DETEMIR
31	DRUGS USED IN DIABETES	DIABETES MELL. TYPE 2	INSULIN LISPRO
32	DRUGS USED IN DIABETES	DIABETES MELL. TYPE 2	METFORMIN
33	DRUGS USED IN DIABETES	DIABETES MELLITIS TYPE 2	EMPAGLIFLOZIN
34	DRUGS USED IN DIABETES	DIABETES MELLITIS TYPE 2	GLIBENCLAMIDE
35	DRUGS USED IN DIABETES	DIABETES MELLITIS TYPE 2	INSULIN DETEMIR
36	DRUGS USED IN DIABETES	DIABETES MELLITIS TYPE 2	INSULIN LISPRO
37	DRUGS USED IN DIABETES	DIABETES MELLITUS	DULAGLUTIDE

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
38	DRUGS USED IN DIABETES	DIABETES MELLITUS	EXENATIDE
39	DRUGS USED IN DIABETES	DIABETES MELLITUS	GLIPIZIDE
40	DRUGS USED IN DIABETES	DIABETES MELLITUS	HUMAN MIXTARD
41	DRUGS USED IN DIABETES	DIABETES MELLITUS	INSULIN ASPART
42	DRUGS USED IN DIABETES	DIABETES MELLITUS	INSULIN DETEMIR
43	DRUGS USED IN DIABETES	DIABETES MELLITUS	INSULIN GLARGINE
44	DRUGS USED IN DIABETES	DIABETES MELLITUS	INSULIN HUMAN
45	DRUGS USED IN DIABETES	DIABETES MELLITUS	INSULIN LISPRO
46	DRUGS USED IN DIABETES	DIABETES MELLITUS	LIRAGLUTIDE
47	DRUGS USED IN DIABETES	DIABETES MELLITUS	METFORMIN
48	DRUGS USED IN DIABETES	DIABETES MELLITUS	METFORMIN HYDROCHLORIDE
49	DRUGS USED IN DIABETES	DIABETES MELLITUS	RISTFOR
50	DRUGS USED IN DIABETES	DIABETES MELLITUS	SITAGLIPTIN PHOSPHATE
51	DRUGS USED IN DIABETES	DIABETES MELLITUS TYP II	INSULIN LISPRO
52	DRUGS USED IN DIABETES	DIABETES MELLITUS TYP II	VELMETIA
53	DRUGS USED IN DIABETES	DIABETES MELLITUS 1	INSULIN GLARGINE
54	DRUGS USED IN DIABETES	DIABETES MELLITUS 1	INSULIN LISPRO
55	DRUGS USED IN DIABETES	DIABETES MELLITUS 11	GLIPIZIDE
56	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	CANAGLIFLOZIN
57	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	DULAGLUTIDE
58	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	EXENATIDE
59	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	GLIBOMET
60	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	GLIMEPIRIDE
61	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	GLIPIZIDE
62	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	HUMAN MIXTARD
63	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	INSULIN ASPART
64	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	INSULIN DETEMIR
65	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	INSULIN GLARGINE
66	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	METFORMIN
67	DRUGS USED IN DIABETES	DIABETES MELLITUS 2	METFORMIN HYDROCHLORIDE
68	DRUGS USED IN DIABETES	DIABETES MELLITUS II	GLIPIZIDE
69	DRUGS USED IN DIABETES	DIABETES MELLITUS II	METFORMIN
70	DRUGS USED IN DIABETES	DIABETES MELLITUS II	SITAGLIPTIN
71	DRUGS USED IN DIABETES	DIABETES MELLITUS TYP 2	METFORMIN
72	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	GLIPIZIDE
73	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	INSULIN GLARGINE
74	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	INSULIN LISPRO
75	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	METFORMIN
76	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	METFORMIN HYDROCHLORIDE
77	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2	SITAGLIPTIN PHOSPHATE
78	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	CANAGLIFLOZIN W/METFORMIN HYDROCHLORIDE
79	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	DULAGLUTIDE
80	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	GLIPIZIDE
81	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	HUMAN MIXTARD
82	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	INSULIN

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
83	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	INSULIN ASPART
84	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	INSULIN DETEMIR
85	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	INSULIN GLARGINE
86	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	INSULIN LISPRO
87	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	METFORMIN
88	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	METFORMIN HYDROCHLORIDE
89	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	NATEGLINIDE
90	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II	SITAGLIPTIN PHOSPHATE
91	DRUGS USED IN DIABETES	DIABETES MELLITUS, TYPE II	METFORMIN HYDROCHLORIDE
92	DRUGS USED IN DIABETES	DIABETES TYPE 2	GLIPIZIDE
93	DRUGS USED IN DIABETES	DIABETES TYPE 2	HUMAN MIXTARD
94	DRUGS USED IN DIABETES	DIABETES TYPE 2	INSULIN ASPART
95	DRUGS USED IN DIABETES	DIABETES TYPE 2	INSULIN DETEMIR
96	DRUGS USED IN DIABETES	DIABETES TYPE 2	INSULIN GLARGINE
97	DRUGS USED IN DIABETES	DIABETES TYPE 2	INSULIN LISPRO
98	DRUGS USED IN DIABETES	DIABETES TYPE 2	KOMBIGLYZE
99	DRUGS USED IN DIABETES	DIABETES TYPE 2	METFORMIN
100	DRUGS USED IN DIABETES	DIABETES TYPE 2	SITAGLIPTIN PHOSPHATE
101	DRUGS USED IN DIABETES	DIABETES TYPE II	METFORMIN
102	DRUGS USED IN DIABETES	DIABETES, TYPE 2	GLIMEPIRIDE
103	DRUGS USED IN DIABETES	DIABETES, TYPE 2	LIRAGLUTIDE
104	DRUGS USED IN DIABETES	DIABETES, TYPE 2	PIOGLITAZONE
105	DRUGS USED IN DIABETES	DIABETIS	INSULIN GLARGINE
106	DRUGS USED IN DIABETES	DM2	GLIPIZIDE
107	DRUGS USED IN DIABETES	DM2	METFORMIN HYDROCHLORIDE
108	DRUGS USED IN DIABETES	HYPERGLICEMIA	GLIPIZIDE
109	DRUGS USED IN DIABETES	HYPERGLYCEMIA	INSULIN HUMAN
110	DRUGS USED IN DIABETES	HYPERGLYCEMIA	METFORMIN
111	DRUGS USED IN DIABETES	HYPERGLYCEMIA	METFORMIN HYDROCHLORIDE
112	DRUGS USED IN DIABETES	HYPERINSULINISM	METFORMIN
113	DRUGS USED IN DIABETES	HYPERTENSION	METFORMIN
114	DRUGS USED IN DIABETES	NONALCOHOLIC STEATOHEPATITIS	METFORMIN
115	DRUGS USED IN DIABETES	TYPE 1 DIABETES	INSULIN DEGLUDEC
116	DRUGS USED IN DIABETES	TYPE 1 DIABETES MELLITUS	INSULIN ASPART
117	DRUGS USED IN DIABETES	TYPE 1 DIABETES MELLITUS	INSULIN GLARGINE
118	DRUGS USED IN DIABETES	TYPE 2 DIABETES	GLICLAZIDE
119	DRUGS USED IN DIABETES	TYPE 2 DIABETES	HUMAN MIXTARD
120	DRUGS USED IN DIABETES	TYPE 2 DIABETES	INSULIN ASPART
121	DRUGS USED IN DIABETES	TYPE 2 DIABETES	INSULIN GLARGINE
122	DRUGS USED IN DIABETES	TYPE 2 DIABETES	INSULIN LISPRO
123	DRUGS USED IN DIABETES	TYPE 2 DIABETES	METFORMIN
124	DRUGS USED IN DIABETES	TYPE 2 DIABETES	METFORMIN HYDROCHLORIDE
125	DRUGS USED IN DIABETES	TYPE 2 DIABETES	SITAGLIPTIN PHOSPHATE
126	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	GLIMEPIRIDE
127	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	HUMAN MIXTARD

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
128	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	INSULIN HUMAN
129	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	LIRAGLUTIDE
130	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	METFORMIN HYDROCHLORIDE
131	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS	PIOGLITAZONE
132	DRUGS USED IN DIABETES	TYPE II DIABETES	CANAGLIFLOZIN W/METFORMIN HYDROCHLORIDE
133	DRUGS USED IN DIABETES	TYPE II DIABETES	DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE W/METFO
134	DRUGS USED IN DIABETES	TYPE II DIABETES	GLIPIZIDE
135	DRUGS USED IN DIABETES	TYPE II DIABETES	INSULIN
136	DRUGS USED IN DIABETES	TYPE II DIABETES	INSULIN DETEMIR
137	DRUGS USED IN DIABETES	TYPE II DIABETES	INSULIN GLARGINE
138	DRUGS USED IN DIABETES	TYPE II DIABETES	LIRAGLUTIDE
139	DRUGS USED IN DIABETES	TYPE II DIABETES	METFORMIN
140	DRUGS USED IN DIABETES	TYPE II DIABETES	SITAGLIPTIN PHOSPHATE
141	DRUGS USED IN DIABETES	TYPE II DIABETES MELLITUS	EXENATIDE
142	DRUGS USED IN DIABETES	TYPE II DIABETES MELLITUS	METFORMIN
143	DRUGS USED IN DIABETES	TYPE II DIABETES MELLITUS	METFORMIN HYDROCHLORIDE
144	DRUGS USED IN DIABETES	UNCONTROLLED DIABETES MELLITUS 2	INSULIN LISPRO
145	DRUGS USED IN DIABETES	UNCONTROLLED DIABETES MELLITUS WITH HYPERGLICEMIA	GLIPIZIDE
146	DRUGS USED IN DIABETES	UNCONTROLLED DIABETES MELLITUS WITH HYPERGLICEMIA	HUMAN MIXTARD
147	DRUGS USED IN DIABETES	UNCONTROLLED DM2	INSULIN DETEMIR
148	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	HERBAL SUPPLEMENT	GLYCINE MAX EXTRACT
149	LIPID MODIFYING AGENTS	DIABETES MELLITUS TYPE II	PRAVASTATIN

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
Cardiovascular (CARDDIS)			
1	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	ACUTE MYOCARDIAL INFARCTION	IRBESARTAN
2	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	CARDIOMYOPATHY	LISINOPRIL
3	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	CARDIOMYOPATHY	RAMIPRIL
4	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	CONGESTIVE HEART FAILURE	LISINOPRIL
5	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	CORONARY ARTERY DISEASE	RAMIPRIL
6	BETA BLOCKING AGENTS	ACUTE MYOCARDIAL INFARCTION	BISOPROLOL FUMARATE
7	BETA BLOCKING AGENTS	ANTI ARRHYTHMIC	SOTALOL
8	BETA BLOCKING AGENTS	ATHEROSCLEROTIC HEART DISEASE OF NATIVE CORONARY ARTERY WITHOUT ANGINA PECTORIS	CARVEDILOL
9	BETA BLOCKING AGENTS	ATRIAL FIBRILATION	ATENOLOL
10	BETA BLOCKING AGENTS	ATRIAL FIBRILATION	METOPROLOL
11	BETA BLOCKING AGENTS	ATRIAL FIBRILLATION	METOPROLOL
12	BETA BLOCKING AGENTS	ATRIAL FIBRILLATION	METOPROLOL TARTRATE
13	BETA BLOCKING AGENTS	ATYPICAL CHEST PAIN	LABETALOL
14	BETA BLOCKING AGENTS	BRUGADA SYNDROME	BISOPROLOL
15	BETA BLOCKING AGENTS	CAD	METOPROLOL SUCCINATE
16	BETA BLOCKING AGENTS	CADRIOMYOPATHY	BISOPROLOL
17	BETA BLOCKING AGENTS	CARDIAC PACEMAKER INSITU	METOPROLOL
18	BETA BLOCKING AGENTS	CARDIAC PROPHYLAXIS	CARVEDILOL
19	BETA BLOCKING AGENTS	CARDIOMYOPATHY	CARVEDILOL
20	BETA BLOCKING AGENTS	CHEST TIGHTNESS	BISOPROLOL
21	BETA BLOCKING AGENTS	CONGESTIVE HEART FAILURE	ATENOLOL
22	BETA BLOCKING AGENTS	CONGESTIVE HEART FAILURE	CARVEDILOL
23	BETA BLOCKING AGENTS	CONTROLLED HYPERTENSION	TENORETIC
24	BETA BLOCKING AGENTS	CORONARY ARTERY DISEASE	METOPROLOL
25	BETA BLOCKING AGENTS	CORONARY ARTERY DISEASE	METOPROLOL SUCCINATE
26	BETA BLOCKING AGENTS	CORONARY ARTERY STENOSIS	METOPROLOL
27	BETA BLOCKING AGENTS	DYSRHYTHMIA	BISOPROLOL FUMARATE
28	BETA BLOCKING AGENTS	HEART FAILURE AND HYPERTENSION	CARVEDILOL
29	BETA BLOCKING AGENTS	INTERMITTENT ARRHYTHMIA	BISOPROLOL
30	BETA BLOCKING AGENTS	MITRAL INSUFFICIENCY	BISOPROLOL
31	BETA BLOCKING AGENTS	PREVENTATIVE FOLLOWING ACUTE MYCARDIAL INFARCTION	BISOPROLOL
32	BETA BLOCKING AGENTS	SICK SINUS SYNDROME	METOPROLOL
33	BETA BLOCKING AGENTS	SUPRA VENTRICULAR TACHYCARDIA	ATENOLOL
34	BETA BLOCKING AGENTS	SUPRAVENTRICULAR TACHYCARDIA	ATENOLOL

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
35	BETA BLOCKING AGENTS	SUPRAVENTRICULAR TACHYCARDIA	METOPROLOL
36	BETA BLOCKING AGENTS	TACHYCARDIA	ATENOLOL
37	CALCIUM CHANNEL BLOCKERS	CORONARY ARTERY DISEASE	AMLODIPINE
38	CALCIUM CHANNEL BLOCKERS	CORONARY ARTERY DISEASE	AMLODIPINE BESILATE
39	CALCIUM CHANNEL BLOCKERS	SUPRAVENTRICULAR TACHYCARDIA	VERAPAMIL
40	CARDIAC THERAPY	ACUTE MYOCARDIAL INFARCTION	AMIODARONE HYDROCHLORIDE
41	CARDIAC THERAPY	ACUTE MYOCARDIAL INFARCTION	ISOSORBIDE DINITRATE
42	CARDIAC THERAPY	ALLERGIC REACTION	EPINEPHRINE
43	CARDIAC THERAPY	ANGINA	GLYCERYL TRINITRATE
44	CARDIAC THERAPY	ANGINA PECTORIS	RANOLAZINE
45	CARDIAC THERAPY	ANGIOGRAM/STENT	ADENOSINE
46	CARDIAC THERAPY	ANGIONEUROTIC EDEMA	EPINEPHRINE
47	CARDIAC THERAPY	ANTIARRHYTHMIC AGENT	FLECAINIDE ACETATE
48	CARDIAC THERAPY	ATRIAL FIBRILLATION	DIGOXIN
49	CARDIAC THERAPY	ATRIAL FIBRILLATION	FLECAINIDE ACETATE
50	CARDIAC THERAPY	ATYPICAL CHEST PAIN	GLYCERYL TRINITRATE
51	CARDIAC THERAPY	CAD	UBIDECARENONE
52	CARDIAC THERAPY	CARDIOMYOPATHY	ISOSORBIDE DINITRATE
53	CARDIAC THERAPY	CARDIOVASCULAR DISEASE PROPHYLAXIS	UBIDECARENONE
54	CARDIAC THERAPY	CHEST PAIN	GLYCERYL TRINITRATE
55	CARDIAC THERAPY	CHEST PAINS	GLYCERYL TRINITRATE
56	CARDIAC THERAPY	CHESTPAIN	GLYCERYL TRINITRATE
57	CARDIAC THERAPY	CORONARY ARTERY DISEASE	GLYCERYL TRINITRATE
58	CARDIAC THERAPY	CORONARY ARTERY DISEASE	ISOSORBIDE MONONITRATE
59	CARDIAC THERAPY	HYPERLIPIDEMIA	ISOSORBIDE MONONITRATE
60	CARDIAC THERAPY	NSTEMI	ISOSORBIDE DINITRATE
61	CARDIAC THERAPY	PERIOP STRESS TEST	REGADENOSON
62	CARDIAC THERAPY	PROPHYLAXIS	GLYCERYL TRINITRATE
63	CARDIAC THERAPY	PROPHYLAXIS FOR CARDIAC HEALTH	UBIDECARENONE
64	CARDIAC THERAPY	SUPRAVENTRICULAR TACHYCARDIA	ADENOSINE
65	CARDIAC THERAPY	UNCONTROLLED DIABETES MELLITUS 2	AMIODARONE HYDROCHLORIDE
66	CARDIAC THERAPY	UNCONTROLLED DIABETES MELLITUS 2	GLYCERYL TRINITRATE
67	DIURETICS	ACUTE RESPIRATORY FAILURE	FUROSEMIDE
68	DIURETICS	AORTIC VALVE REPLACEMENT	FUROSEMIDE
69	DIURETICS	CHF	BUMETANIDE
70	DIURETICS	CHF	HYDROCHLOROTHIAZIDE
71	DIURETICS	CHF	METOLAZONE
72	DIURETICS	CONGESTIVE HEART FAILURE	BUMETANIDE
73	DIURETICS	CONGESTIVE HEART FAILURE	FUROSEMIDE

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
74	DIURETICS	CONGESTIVE HEART FAILURE	HYDROCHLOROTHIAZIDE
75	DIURETICS	CONGESTIVE HEART FAILURE	METOLAZONE
76	DIURETICS	CONGESTIVE HEART FAILURE	SPIRONOLACTONE
77	DIURETICS	CORONARY ARTERY DISEASE	HYDROCHLOROTHIAZIDE
78	DIURETICS	CORONARY ARTERY DISEASE.	FUROSEMIDE
79	DIURETICS	ELEVATION OF BLOOD PRESSURE	FUROSEMIDE
80	DIURETICS	MITRAL INSUFFICIENCY	TORASEMIDE
81	DIURETICS	TRANSGENGER	SPIRONOLACTONE
82	LIPID MODIFYING AGENTS	ACUTE MYOCARDIAL INFARCTION	ATORVASTATIN CALCIUM
83	LIPID MODIFYING AGENTS	ACUTE MYOCARDIAL INFARCTION	OMEGA 3 TRIGLYCERIDES
84	LIPID MODIFYING AGENTS	ATHEROSCLEROTIC HEART DISEASE OF NATIVE CORONARY ARTERY WITHOUT ANGINA PECTORIS	SIMVASTATIN
85	LIPID MODIFYING AGENTS	BASILAR ARTERY THROMBUS	ATORVASTATIN CALCIUM
86	LIPID MODIFYING AGENTS	CAD	PRAVASTATIN SODIUM
87	LIPID MODIFYING AGENTS	CAD	ROSUVASTATIN CALCIUM
88	LIPID MODIFYING AGENTS	CARDIAC PROPHYLAXIS	ATORVASTATIN
89	LIPID MODIFYING AGENTS	CARDIAC PROPHYLAXIS	FISH OIL
90	LIPID MODIFYING AGENTS	CARDIOVASCULAR PROPHYLAXIS	ATORVASTATIN CALCIUM
91	LIPID MODIFYING AGENTS	CHEST TIGHTNESS	ATORVASTATIN

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
Hyperlipidemia (HLIPDEM)			
1	AGENTS ACTING ON THE RENIN ANGIOTENSIN SYSTEM	HYPERTRIGLYCERIDEMIA	LISINOPRIL
2	ANTIHYPERTENSIVES	HYPERCHOLESTEROLEMIA	DOXAZOSIN MESILATE
3	CARDIAC THERAPY	HYPERCHOLESTEROLEMIA	UBIDECARENONE
4	LIPID MODIFYING AGENTS	ABNORMAL LIPIDS	ATORVASTATIN
5	LIPID MODIFYING AGENTS	CARDIAC PROPHYLAXIS	ROSUVASTATIN
6	LIPID MODIFYING AGENTS	CHOLESTEROL	ROSUVASTATIN
7	LIPID MODIFYING AGENTS	CHOLESTEROL	ROSUVASTATIN CALCIUM
8	LIPID MODIFYING AGENTS	CHOLESTEROLEAMIA	ATORVASTATIN
9	LIPID MODIFYING AGENTS	CHOLESTERORL	ROSUVASTATIN CALCIUM
10	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE	ATORVASTATIN
11	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE	EZETIMIBE
12	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE	FENOFIBRATE
13	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE	ROSUVASTATIN CALCIUM
14	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE PROPHYLAXIS	ATORVASTATIN
15	LIPID MODIFYING AGENTS	DIET SUPPLEMENT	FISH OIL
16	LIPID MODIFYING AGENTS	DIETARY SUPPLEMENT	FISH OIL
17	LIPID MODIFYING AGENTS	DIETARY SUPPLEMENTS	FISH OIL
18	LIPID MODIFYING AGENTS	DYSLIPEDEMIA	ROSUVASTATIN CALCIUM
19	LIPID MODIFYING AGENTS	DYSLIPIDAEMIA	ATORVASTATIN
20	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	ATORVASTATIN
21	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	FENOFIBRATE
22	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	FISH OIL
23	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	GEMFIBROZIL
24	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	PRAVASTATIN
25	LIPID MODIFYING AGENTS	DYSLIPIDEMIA	ROSUVASTATIN
26	LIPID MODIFYING AGENTS	DYSLIPIDEMIA, WORSENING	ROSUVASTATIN
27	LIPID MODIFYING AGENTS	DYSLIPIDERMIA	PRAVASTATIN
28	LIPID MODIFYING AGENTS	ELEVATED CHOLESTEROL	SIMVASTATIN
29	LIPID MODIFYING AGENTS	ELEVATED LIPIDS	ATORVASTATIN
30	LIPID MODIFYING AGENTS	ELEVATED LIPIDS	ATORVASTATIN CALCIUM
31	LIPID MODIFYING AGENTS	ELEVATED TRIGLYCERIDES	FISH OIL
32	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	ATORVASTATIN
33	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	ATORVASTATIN CALCIUM
34	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	GEMFIBROZIL
35	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	LOVASTATIN
36	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	PRAVASTATIN
37	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	ROSUVASTATIN CALCIUM
38	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	SIMVASTATIN
39	LIPID MODIFYING AGENTS	HIGH CHOLESTROL	ATORVASTATIN
40	LIPID MODIFYING AGENTS	HIGH PLASMA LIPIDS	ATORVASTATIN
41	LIPID MODIFYING AGENTS	HIGH TRIGLYCERIDES	FENOFIBRATE
42	LIPID MODIFYING AGENTS	HIGH TRIGLYCERIDES AND HYPERCHOLESTEROLEMIA	ATORVASTATIN
43	LIPID MODIFYING AGENTS	HIPERCOLESTEROLEMIA	ATORVASTATIN

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
44	LIPID MODIFYING AGENTS	HIPERCOLESTEROLEMIA	ATORVASTATIN CALCIUM
45	LIPID MODIFYING AGENTS	HIPERCOLESTEROLEMIA	SIMVASTATIN
46	LIPID MODIFYING AGENTS	HYERLIPIDEMIA	OMEGA 3 ACID ETHYL ESTER
47	LIPID MODIFYING AGENTS	HYPERCHOLESTERIMIA	FENOFIBRATE
48	LIPID MODIFYING AGENTS	HYPERCHOLESTERINAEMIA	ATORVASTATIN
49	LIPID MODIFYING AGENTS	HYPERCHOLESTERINAEMIA	PRAVASTATIN
50	LIPID MODIFYING AGENTS	HYPERCHOLESTERINEMIA	PRAVASTATIN
51	LIPID MODIFYING AGENTS	HYPERCHOLESTERINEMIA	SIMVASTATIN
52	LIPID MODIFYING AGENTS	HYPERCHOLESTEROL	PRAVASTATIN
53	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLAEMIA	ATORVASTATIN
54	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLAEMIA	PRAVASTATIN
55	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLAEMIA	ROSUVASTATIN
56	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLAEMIA	SIMVASTATIN
57	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	ATORVASTATIN
58	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	ATORVASTATIN CALCIUM
59	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	EZETIMIBE
60	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	FENOFIBRATE
61	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	FISH OIL
62	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	LOVASTATIN
63	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	PITAVASTATIN CALCIUM
64	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	PRAVASTATIN
65	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	PRAVASTATIN SODIUM
66	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	ROSUVASTATIN
67	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	ROSUVASTATIN CALCIUM
68	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	SIMVASTATIN
69	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA (PURE) AND MIXED HYPERLIPIDEMIA	ROSUVASTATIN CALCIUM
70	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLMIA	PRAVASTATIN SODIUM
71	LIPID MODIFYING AGENTS	HYPERCHOLESTROLEMIA	ATORVASTATIN
72	LIPID MODIFYING AGENTS	HYPERCHOLESTROLEMIA	ATORVASTATIN CALCIUM
73	LIPID MODIFYING AGENTS	HYPERCHOLESTROLEMIA	FENOFIBRATE
74	LIPID MODIFYING AGENTS	HYPERCHOLSTEROAEMIA	ATORVASTATIN CALCIUM
75	LIPID MODIFYING AGENTS	HYPERCOLESTEROLEMIA	SIMVASTATIN
76	LIPID MODIFYING AGENTS	HYPERLIDEMIA	ROSUVASTATIN CALCIUM
77	LIPID MODIFYING AGENTS	HYPERLIDIPEMIA	ATORVASTATIN
78	LIPID MODIFYING AGENTS	HYPERLIPDEMIA	ROSUVASTATIN CALCIUM
79	LIPID MODIFYING AGENTS	HYPERLIPEDMIA MIXED	ATORVASTATIN
80	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	ATORVASTATIN
81	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	FENOFIBRATE
82	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	PRAVASTATIN
83	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	PRAVASTATIN SODIUM
84	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	ROSUVASTATIN
85	LIPID MODIFYING AGENTS	HYPERLIPIDAEMIA	ROSUVASTATIN CALCIUM
86	LIPID MODIFYING AGENTS	HYPERLIPIDEMA	ATORVASTATIN
87	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	ATORVASTATIN
88	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	ATORVASTATIN CALCIUM

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
89	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	COLESEVELAM HYDROCHLORIDE
90	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	EICOSAPENTAENOIC ACID ETHYL ESTER
91	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	EZETIMIBE
92	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	FENOFIBRATE
93	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	FENOFIBRIC ACID
94	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	FISH OIL
95	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	GEMFIBROZIL
96	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	LOVASTATIN
97	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	OMEGA 3 ACID ETHYL ESTER
98	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	PELAGO
99	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	PRAVASTATIN
100	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	PRAVASTATIN SODIUM
101	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	ROSUVASTATIN
102	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	ROSUVASTATIN CALCIUM
103	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	SIMVASTATIN
104	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA PREVENTION	ROSUVASTATIN CALCIUM
105	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA,	PRAVASTATIN
106	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA, MIXED	ATORVASTATIN CALCIUM
107	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA, MIXED	FENOFIBRATE
108	LIPID MODIFYING AGENTS	HYPERTENSION	ATORVASTATIN
109	LIPID MODIFYING AGENTS	HYPERTENSION	PRAVASTATIN
110	LIPID MODIFYING AGENTS	HYPERTRIGLYCERDEMIA	ATORVASTATIN
111	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	ATORVASTATIN CALCIUM
112	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	FENOFIBRATE
113	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	FENOFIBRIC ACID
114	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	FIBRATES
115	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	FISH OIL
116	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	OMEGA 3 TRIGLYCERIDES
117	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA	PRAVASTATIN
118	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA,HYPERCHOLESTEROLEMIA	ATORVASTATIN
119	LIPID MODIFYING AGENTS	HYPERTRIGLYERIDEMIA	GEMFIBROZIL
120	LIPID MODIFYING AGENTS	HYPERTRYGLYCERIDEMIA	PRAVASTATIN
121	LIPID MODIFYING AGENTS	INDICATION HYPERLIPIDEMIA	FENOFIBRATE
122	LIPID MODIFYING AGENTS	IRRITABLE BOWEL SYNDROME	FISH OIL
123	LIPID MODIFYING AGENTS	ISCHEMIC HEART DISEASE	ROSUVASTATIN CALCIUM
124	LIPID MODIFYING AGENTS	LDL CHOLESTEROL GRADE 3 ELEVATION	ROSUVASTATIN
125	LIPID MODIFYING AGENTS	MIXED DYSLIPIDEMIA	FENOFIBRATE
126	LIPID MODIFYING AGENTS	MIXED DYSLIPIDEMIA	ROSUVASTATIN CALCIUM
127	LIPID MODIFYING AGENTS	MIXED HYPERLIPDEMIA	ATORVASTATIN
128	LIPID MODIFYING AGENTS	MIXED HYPERLIPIDEMIA	ATORVASTATIN
129	LIPID MODIFYING AGENTS	MIXED HYPERLIPIDEMIA	FENOFIBRATE
130	LIPID MODIFYING AGENTS	MIXED HYPERLIPIDEMIA	GEMFIBROZIL
131	LIPID MODIFYING AGENTS	NUTRITION SUPPLEMENT	FISH OIL

	Medication Class (WHOATC2)	Indication (CMINDC)	WHOGEN
132	LIPID MODIFYING AGENTS	NUTRITIONAL SUPPLEMENT	FISH OIL
133	LIPID MODIFYING AGENTS	NUTRITIONAL SUPPLEMENT	OMEGA 3 FATTY ACIDS
134	LIPID MODIFYING AGENTS	PREVENTATIVE FOLLOWING ACUTE MYCARDIAL INFARCTION	ATORVASTATIN
135	LIPID MODIFYING AGENTS	PREVENTION FOR HYPERCHOLESTEROLEMIA	OMEGA 3 FATTY ACIDS
136	LIPID MODIFYING AGENTS	PREVENTIVE	FISH OIL W/LINUM USITATISSIMUM SEED OIL
137	LIPID MODIFYING AGENTS	PROPHYLAXIS	FISH OIL
138	LIPID MODIFYING AGENTS	PURE HYPERCHOLESTEROLEMIA	ATORVASTATIN
139	LIPID MODIFYING AGENTS	SECONDARY STROKE PREVENTION	ATORVASTATIN
140	LIPID MODIFYING AGENTS	STROKE PROPHYLAXIS	ATORVASTATIN
141	LIPID MODIFYING AGENTS	SUPPLEMENT	FISH OIL
142	LIPID MODIFYING AGENTS	SUPPLEMENT	OMEGA 3 6 9
143	LIPID MODIFYING AGENTS	SUPPLEMENT	OMEGA 3 FATTY ACIDS
144	LIPID MODIFYING AGENTS	SUPPLEMENT	OMEGA 3 FATTY ACIDS W/OMEGA 6 FATTY ACIDS
145	LIPID MODIFYING AGENTS	SUPPLEMENT	OMEGA 3 ACID ETHYL ESTER
146	LIPID MODIFYING AGENTS	SUPPLEMENT/HYPERLIPIDEMIA	FISH OIL
147	LIPID MODIFYING AGENTS	SUPPLEMENTAL USE	FISH OIL
148	LIPID MODIFYING AGENTS	SUPPLEMETN	FISH OIL
149	LIPID MODIFYING AGENTS	UNCONTROLLED DIABETES MELLITUS 2	ATORVASTATIN
150	LIPID MODIFYING AGENTS	WORSENING HYPERLIPIDEMIA	ATORVASTATIN
151	LIPID MODIFYING AGENTS	WORSENING OF HYPERLIPIDEMIA	FISH OIL
152	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL	NICOTINIC ACID
153	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA	NICOTINIC ACID
154	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA	NICOTINIC ACID
155	LIPID MODIFYING AGENTS	MIXED HYPERLIPIDEMIA	NICOTINIC ACID

Appendix 12. Programming Specification

1) AGE calculated as follows:

   a) AGE (years) is calculated from the number of days between the date of birth (DOB) and Day 1 (first dose date),

   b) Use the SAS INTCK function to determine the number of "1st-of-month days" (ie, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),

   c) Divide the result in (b) by 12,

   d) AGE the integer of the result in (c),

   e) If the DOB and Day 1 have the month in common and the birthday is later in the month than the date of Study Day 1, then subtract one from the AGE result above.

2) For subjects randomized and never dosed with study drug, age will be calculated from the date of randomization.

3) All screened subjects refer to all subjects who are screened (ie, with nonmissing screening date) and have a screening number. For summaries, the same subject is counted only once. DOB and other demographic information such as sex, race, ethnicity, country, and initials will be used to identify unique screened subjects.

4) Screen failure subjects are the subjects who are screened and answered "No" for any inclusion criteria or "Yes" for any exclusion criteria regardless of which version of protocol the subject was consent to.

5) Subjects in the randomized analysis set are defined as subjects randomized into the study. IXRSRAND is the source to determine whether the subject is randomized (ie, subject with nonmissing RGMNDTN in the IXRSRAND dataset) and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN "Yes" in ENROLL dataset).

6) Randomized treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if subject took at least 1 dose of study drug and assigned as blank if subject never dosed.

7) In disposition table, the reasons for premature discontinuation are displayed in the order as they appear on the eCRF.

8) Only 1 study completion form is collected for the entire study. Therefore, study disposition in the DB phase of the study is defined as follows for dosed subjects:

   f) Subjects who completed study in the DB phase are defined as follows:

      i) Open-label entry eCRF marked as "Yes", OR

      ii) Open-label phase first dose date is present, OR

      iii) Study completion form is marked as "Yes".

   g) Subjects who are ongoing in the DB phase of the study is defined as subjects who have not entered the OLE phase of the study, DB phase study drug completion form is marked as "N" or missing, and study completion form is also missing.

   h) Subjects not meeting (a) and (b) above will be the subjects who discontinued study in the DB phase of the study.

9) Body mass index (BMI) will be calculated only at baseline as follows:

- BMI (weight [kg]) / (height [meters]^2)

  Baseline height and weight will be used for this calculation.

10) For summaries using the PK Case-Control Analysis Set by HIV infection cases versus uninfected matched controls, if one subject serves as both as case and control, this subject will be summarized under both the HIV infection case and uninfected matched control columns.

11) SAS codes for the treatment comparison for demographics and baseline characteristics tables.

   i) CMH test for nominal variable (Y), the p-value from general association test should be used for nominal variable (including race, ethnicity, education, employment, sexuality, number of subjects with a syphilis diagnosis, circumcision, geography, and dichotomous variables):

```
proc freq data=adsl;
   tables trtgrp * Y /cmh /*general association test*/
run;
```

j) CMH test for ordinal variable (Y), the p-value from row mean score test should be used for ordinal variable (including the number of subjects with each STI lab test result type, ongoing relationship, AUDIT questions or total score, proteinuria toxicity grade by urinalysis and categorical summaries of any continuous variables like age, adherence rate or number of partners):

```
proc freq data=adsl;
   tables trtgrp * Y / cmh2 score=modridit; /*row mean score test*/
run;
```

k) Wilcoxon rank sum test for continuous variable (Y), the p-value from the normal approximation 2-sided test should be used for continuous variable:

```
proc npar1way wilcoxon data=adsl;
   class trtgrp;
   var Y;
run;
```

l) Van Elteren test stratified by baseline F/TDF for PrEP:

```
proc freq data=test;
table bftdf*trt*outcome/cmh2 scores=modridit;
run;
```

Where bftdf is baseline F/TDF for PrEP (yes or no), trt is treatment, and outcome is the % change or change from baseline depending on endpoint of interest. Please report p-value from row mean scores differ.

12) Please note, “Not Permitted”, “Unknown”, “Not Applicable”, “Not Done” or missing categories will be excluded for percentage calculation and also excluded for p-value generation for categorical data analysis (ie, CMH test or Fisher exact test). For the number of subjects with each syphilis stage and syphilis status summarized among subjects with a syphilis diagnosis, no p-values will be generated.

13) SAS code for the treatment comparison for duration of exposure. The p-value from log rank test should be used.

```
proc lifetest data=ADSL method=km;
   time TRTDURD*ESDD(0); /*Derive ESDD from COMT01FL, where ESDD = 0
   indicates censored observation (ie, subject is still on study drug)*/
   Strata TRT01AN;
   label TRTDURD = "Duration of Exposure (Days)";
run;
```

14) Last Dose Date and Last Study Date

a) Last Dose Date (ie, TRTEDTC, TRTEDT, TR01EDT or TR01EDTC) in ADSL was defined in Section 3.8.1 for subjects who prematurely discontinued or completed study drug in the ‘blinded treatment’ study phase.

If study drug start date or end date are partially missing (ie, only year and month are known), the day will be imputed as 15 for the purpose of this analysis.

For subjects with a partial last dosing date (ie, month and year of last dose are known), use the max (the dispensing dates of study drug bottles, study drug start dates and end dates, imputed end date of last dose [day imputed as 15]) as the final imputed last dose date. (However, if dispensing date's month is after last dose date's month, data query is needed.)

For subjects where only the year of the last dosing date is known), then impute the last dose date based on the below:

Condition	Last dose date (year only) is imputed as
The year of the last dose is equal to the year of the last visit*	Maximum of study drug start dates and end dates, clinic visit dates and laboratory visit dates excluding the 30-day follow-up visit
The year of the last dose is before the year of the last visit*	December 31st of the last dose year
The year of the last dose is after the year of the last visit*	Data query is needed. If this remains unchanged after query, impute as: January 1st of the last dose year

*Last visit is defined as the maximum of clinic visit dates and laboratory visit dates excluding the 30 day follow up visit.

If the date of last dose is completely missing, use the maximum of study drug start dates and end dates, clinic visit dates, and laboratory visit dates excluding the 30-day follow-up visit to impute the last dose date.

If subject died and the death date is complete (ie, not partial date) and before the imputed last dose date, the complete death date should be used as the imputed last dose date.

If subject has been diagnosed with HIV infection and before the imputed last dose date (year only or month/year only known), the date of HIV diagnosis should be used as the imputed last dose date. Per study design, subjects that have been diagnosed with HIV infection must immediately discontinue study drug.

Last Dose Date Imputation for Subjects who are Ongoing on Study Drug Subjects (for the purpose of duration of exposure)

Last dose date is not defined for subjects still on study drug in SAP. However, for the calculation of the duration of exposure to study drug, for subjects who have not permanently discontinued study drug at the time of the data cut date, the estimated last dose date will be the maximum of nonmissing study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding the date of 30-day follow-up visit.

b) Last Study Date is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for subjects who prematurely discontinued study or who completed study according to the Study Completion eCRF. If study drug start dates or end date is partially missing (ie, only year and month are known), the day will be imputed as 15 for the purpose of this analysis.

   If subject died and the death date is complete (ie, not partial date) and before the imputed last study date, the complete death date should be used as the imputed last study date.

   Last Study Date Imputation for Ongoing Subjects

   Last study date is not defined for subjects still on study in SAP. However, for programing purposes, the latest of study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, will be used to impute the last study date for subjects still on study.

15) For the purpose of calculating study drug interruptions, the start date of an interruption is the previous study drug administration end date + 1 day and end date of an interruption is the next time consecutive study drug administration start date - 1 day.

16) Efficacy analyses:

Covance HIV Laboratory Tests

HIV Test Description	HIV-1 Positive results	HIV-1 Negative results	LBTEST	LBTESTCD
HIV-1/HIV-2 screening test (Ag/Ab - 4th generation)	Repeatedly Reactive	Non-reactive	'HIV 1/2 Ag/Ab Screen, Siemens'	CNT449
HIV-1/HIV-2 screening test (Ab - 3rd generation)	Repeatedly Reactive	Non-reactive	'Ab to HIV Type1/Type2-QT'	CNT425
HIV-1/HIV-2 Discrimination Ab test	HIV-1 Positive, HIV2 Pos-HIV1 Cross-reactive, HIV Positive Untypable, 'HIV-2 positive, HIV-1 cross reactive'	HIV Negative, HIV-1 Indeterminate, HIV-2 Indeterminate, HIV Indeterminate, HIV-2 Positive, HIV Antibody Negative	'HIV Ab Interpretation, Geenius'	IMT1948
HIV-1 Qualitative, RNA	Positive	Negative, or Invalid	'HIV-1 RNA Qual,EDTApl-335'	ORT11277
HIV-1 Quantitative RNA	<20 cp/mL HIV-1 RNA Detected or numeric value	No HIV-1 RNA detected,	'HIV RNA TaqMan-2.0-EDTA-CL'	GET1816

a) For the primary efficacy analysis, the HIV infection incidence rate between F/TAF and F/TDF and its 95.003% or 95% CIs are calculated using the rate ratio method. To test superiority, the p-value from 2-sided test should be used, where trtgrp is the treatment, sero is the number of HIV infection events and ln is the natural log of the summation of all subjects' person years follow-up time. The following SAS code will be used to compute the HIV infection incidence rate and p-value.

```
data rate;
   input ptyr sero trtgrp$ ptvd $;
   ln = log(ptyr);
   datalines;
   1500  17  FTAF Y
   1500  16  FTDF Y
   3500  35  FTAF N
   3500  34  FTDF N ;
proc genmod data=rate;
   class trtgrp (ref='FTDF');
   model sero = trtgrp / dist=poisson link=log offset=ln;
   lsmeans trtgrp / ilink diff exp cl alpha=0.04997;
run;
```

b) For a sensitivity analysis, the HIV infection incidence rate between F/TAF and F/TDF and its 95% exact CIs are calculated using the rate differences method. All references to 95% exact CIs are calculated using the method proposed by Ulm. The following SAS code will be used:

```
/*Hybrid CI*/
data test;
   alpha=0.025;
   zval =  quantile("Normal", alpha);

   x1=42; *Number of HIV Infections in F/TAF arm;
   x2=101; *Number of HIV Infections in F/TDF arm;
   f1=500; *Total Person Years Follow Up in F/TAF arm;
   f2=400; *Total Person Years Follow Up in F/TDF arm;

    hat1 = x1/f1;
    hat2 = x2/f2;
    diff = hat1   hat2;

      /*Rate Difference: Hybrid CI*/
    l1   quantile("CHISQ", alpha, 2*x1)/(2*f1); *Ulm lower exact CI;
    u1   quantile("CHISQ", 1-alpha, 2*x1+2)/(2*f1); *Ulm upper exact CI;
    l2   quantile("CHISQ", alpha, 2*x2)/(2*f2); *Ulm lower exact CI;
    u2   quantile("CHISQ", 1-alpha, 2*x2+2)/(2*f2); *Ulm upper exact CI;
    hybriddifflower   hat1 - hat2 - sqrt((hat1 - l1)**2 + (u2 - hat2)**2);
*Lower CI of Rate Difference (F/TAF-F/TDF);
    hybriddiffupper   hat1 - hat2 + sqrt((hat1 - u1)**2 + (l2 - hat2)**2);
*Upper CI of Rate Difference (F/TAF-F/TDF);
run;
```

d) The FAS and PP populations are based on HIV lab test results from either Covance or the Rapid HIV-1/2 Result (LB-HIVDX) eCRF, excluding the Other Local Labs eCRF.

e) From the Other Local Labs eCRF:

i) HIV tests will be classified as follows:

LBTEST name includes keywords for	LBTEST name includes	LBTEST name excludes	CDISCTCD	CDISCTNM
HIV-1	'RNA QUAL',		HIV1RNA	HIV-1 RNA
	'RNA QUAN',		HIVVLD	HIV Viral Load
	'HIV-1 RNA, TMA (QUALITATIVE)'		HIV1RNA	HIV-1 RNA
	'ANTIBODY' 'ANTIBODIES' or '3RD'	'ANTIGEN' or 'ANTIGENS'	HIV1AB	HIV-1 Antibody
HIV-2			HIV2AB	HIV-2 Antibody
HIV-1/2			HIV12AB	HIV-1/2 Antibody
HIV 1/2	'HIV 1/2 AB DIFFERENTIAL WITH REF'		HIV12AB	'HIV-1/2 Antibody'
HIV-1	'ANTIGEN' or 'ANTIGENS'	'ANTIBODY' 'ANTIBODIES' or '3RD'	HIV124AG	HIV-1 p24 Antigen
HIV-1/2	('ANTIBODY' or 'ANTIBODIES') and ('ANTIGEN' or 'ANTIGENS') Or '4TH'		HIV12AGB	HIV-1/2 Antigen/Antibody
HIV1,2	'HIV 1,2 AG/AB 4TH GENERATION'		HIV12AGB	HIV-1/2 Antigen/Antibody
'RAPID'			HIVSERO	HIV-1/2 Antibody and/or Antigen
Self-reported HIV test*			HIVGEN	HIV General

HIV 1/2 includes keywords of 'HIV 1/2' 'HIV 1/2' 'HIV1/2' 'HIV 1&2' "HIV 1&2' 'HIV1&2' 'HIV 1 AND HIV 2' or 'HIV1,2'
HIV 1 includes keywords of 'HIV 1' 'HIV 1' or 'HIV1'
HIV 2 includes keywords 'HIV 2' 'HIV 2' or 'HIV2'
* Note subject PPD self reported HIV based on other local laboratory data tested outside of the site, HIV test name/type was unknown.

	Positive Results includes the following keywords	Negative Results includes the following keywords
CDISCTNM = HIV Viral Load	<20 cp/mL HIV-1 RNA Detected or numeric value	No HIV-1 RNA detected
Other HIV lab tests	Contains Detected, Abnormal, Positive, Reactive (without Not or Non)	Contains Undetected, Not Detected, Negative, Non-reactive, Normal, Inconclusive, Indeterminate

ii) Overall RAPID test results will be derived from the Other Local Lab eCRFs as:

Initial Test	Confirmation Test	Overall Result
Only negative	Missing or only negative	Negative
Any positive	Only negative	Negative
Any positive	Any positive or only missing	Positive

Positive refers to results of 'positive' or 'reactive'
Negative refers to results of 'negative' or 'non reactive'

f) Logarithmic (base 10) transformations will be applied to HIV-1 RNA data for virology datasets.

17) DXA Analysis:

a) Variable used for analysis:

- Variable CORRBMD when Region "SpineTotalAdequate" for spine, Region "FemurTotal" for hip, and Region "FemurNeck" for femur neck will be used for percentage change from baseline in BMD analysis.
- Variable CORRTSCR_M when Region "SpineTotalAdequate" for spine and Region "FemurTotal" for hip will be used for defining the BMD clinical status.

b) ANOVA model for continuous variable: The differences in changes from baseline in BMD between treatment groups and the associated 95% CI will be constructed using an ANOVA, including baseline F/TDF for PrEP and treatment as fixed effects in the model.

```
proc glm data=adeff;
   class bftdf trtgrp;
   model BMD= bftdf trtgrp;
   lsmeans trtgrp /alpha=0.05 cl pdiff;
run;
```

c) For clinical BMD status, the following codes will be used to compute the p-values for comparing the two treatment groups using rank analysis of covariance adjusting for the baseline F/TDF for PrEP and baseline clinical BMD status:

```
proc rank data=BMD nplus1 ties=mean out=ranks;
   by bftdf;
   var BMDstatus Basestatus;
run;

proc reg data=ranks noprint;
   by bftdf;
   model BMDstatus=Basestatus;
   output out=residual r=resid;
run;

proc freq data=residual;
   tables bftdf * treatment * resid/noprint cmh2;
run;
```

d) For categories of percentage change from baseline in the hip BMD and spine BMD, the distribution difference in these categories (based on equidistant scores for each category) between the treatment groups will be compared using CMH test (row mean scores differ statistic) adjusting for baseline F/TDF for PrEP. SAS codes for treatment comparison will be:

```
proc freq order=data;
   tables bftdf * treatment * Y / cmh2 ; /*row mean score test*/
run;
```

18) For the distribution of UP and UPCR categories (or treatment-emergent proteinuria), the following codes will be used to compute the p-values for comparing the two treatment groups using rank analysis of covariance adjusting for baseline F/TDF for PrEP and baseline UP/UPCR categories:

```
proc rank data=UPCR nplus1 ties=mean out=ranks;
   by bftdf;
   var UPCRstatus Basestatus;
run;

proc reg data=ranks noprint;
   by bftdf;
   model UPCRstatus=Basestatus;
   output out=residual r=resid;
run;

proc freq data=residual;
   tables bftdf * treatment * resid/noprint cmh2;
run;
```

19) For prescribed adherence based on pill counts (Section 4.2.3.1), any bottles dispensed after the end date would not be counted into the adherence calculation.

20) LOCF and BlOCF will not be applied at a visit for a subject who is both missing on-treatment values at a visit and has not reached the upper limit of the analysis window for that corresponding visit. For the determination of whether a subject has reached the upper limit of the analysis window, the (1) lab transfer date for lab parameters or (2) DXA transfer date for BMD values will be compared to the upper limit of the analysis window.

21) For CASI summaries of

a) Adherence while on on-treatment (through the last dose date) includes all visits for subjects that are ongoing on study drug and visits occurring through the upper limit of the analysis window corresponding to the date of permanent discontinuation of study drug for subjects that permanently discontinued study drug. (ie. if the last dose date is Day 250, this falls in the Week 36 analysis window and all CASI visits through Day 294 will be included.)

b) Intercourse partners while at risk of HIV infection (through the last at-risk of HIV infection date) includes visits occurring through the upper limit of the analysis window corresponding to the last at-risk of HIV infection date for each subject.

22) TEAE

Events with Missing Onset Day and/or Month

An AE is treatment emergent if the following 3 criteria are met:

1) The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of study drug, and
2) The month and year (or year) of the onset date is the same as or before the month and year (or year) of the 30th day after the date of the last dose of study drug, and
3) End date is as follows:
    a) The (complete) end date is on or after the first dose date, or
    b) The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of study drug, or
    c) End date is completely missing or AE is ongoing

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as TEAE if end date meets any of the criteria specified in 3) above.

23) TEAE incidence rate and prevalence rate:

If the AE onset date or stop date is incomplete and not ongoing, then day will be imputed as the 15th of the month when only month and year are available and the day and month will be imputed as July 1st when only year is available. The imputed AE end date will be refined as the maximum of (AE onset date, imputed AE end date). The imputed AE onset date will be refined as the minimum of (the maximum of [first dose date, imputed AE onset date], AE stop date).

If the AE stop date is unknown (both AE stop date and ongoing status are missing even after query) or ongoing, the AE end date will be imputed with the last dose date.

24) Renal related laboratory ratios were calculated at Covance, but recalculated at Gilead in order to increase the decimal place precision to match those previously reported in other Gilead HIV treatment studies.
    a) Differences in the computation methods between Covance and Gilead, respectively, include :
        i) renal ratios computed using SI units in EU sites which were converted to conventional (CNV) units (Covance) vs. renal ratios computed using only CNV units (Gilead)
        ii) for urine creatinine in the computation of renal ratios, use of original unrounded instrument values (Covance) vs. rounded reported Covance values (Gilead)
        iii) differences in handling of < LOQ values for the individual lab components used to compute the ratios.

Further details are outlined below.

Differences in the Handling of the Individual Lab Components Used for the Computation of the Renal Ratios

Differences	Covance Computed	Gilead Computed
Units	North American accession numbers (beginning with '65'): uses component values in conventional units to compute renal ratios EU accession numbers (beginning with '62'): uses component values in SI units to compute renal ratios then applies a conversion factor to convert the creatinine SI units into conventional units (0.00884 mmol/mg) For urine Beta 2 microglobulin to creatinine ratio, the mg/mmol SI units were converted to mg/mg conventional units by multiplying by 0.00884. ie. Urine Beta 2 microglobulin (mg/L) / creatinine (mmol/L) 1 mg/mmol x 0.00884 mmol/mg 0.00884 mg/mg For UPCR, the mg/mmol SI units were converted to conventional units by multiplying by 0.00884 ie. [Urine protein (mg/dL) / creatinine (mmol/L)] x 10 dL/L 10 mg/mmol x 0.00884 mmol/mg 10 x 0.00884 mg/mg For Urine RBP to creatinine ratio, the ug/mmol SI units were converted to conventional units by multiplying by 0.00884 ie. Urine RBP (ug/L) / creatinine (mmol/L) 1 ug/mmol x 0.00884 mmol/mg (1/1000) x 0.00884 mg/mg	Uses component values in conventional units to compute renal ratios
Rounded values for urine creatinine	Uses measured unrounded result from the instrument 2 decimal places in mg/dL (CNV) 3 decimal places in mmol/L (SI)	Uses the rounded result reported in Covance datasets 0 decimal places in mg/dL (CNV) 2 decimal places in mmol/L (SI)
Imputations for < LOQ	Uses LOQ values in the calculation of related ratios and reapplies the < sign to the final value.	For urine creatinine, values of "< 1" are handled as missing values in the calculation of related ratios. For urine RBP (ug/L), values of "<18.000" are treated as 17.999 in the calculation of renal ratios. For urine Beta 2 microglobulin (mg/L), values of "<0.010" are treated as .009 in the calculation of renal ratios.
UPCR	Calculated for all subjects, even when urine protein < 4.0 mg/dL	Only calculated when urine protein ≥ 4.0 mg/dL

b) Renal related laboratory evaluation (Gilead- computed values)

i) Unit conversion for renal safety tests derived from related tests with conventional units

- Urine RBP (ug/L) to creatinine (mg/dL) ratio: 1 (ug/L) / (mg/dL) 100 × ug/g
- Urine Beta-2-microglobulin (mg/L) to creatinine (mg/dL) ratio: 1 (mg/L) / (mg/dL) 10^5 ug/g

ii) Calculation of ratios:

To calculate laboratory ratios (ie, urine RBP to creatinine ratio), the lab value of each test in the ratio needs to be from the same accession number; if any test value used for the ratio calculation from the same accession number is missing, then the ratio is not calculable (ie, missing).-For urine creatinine, a value of "< 1" is handled as a missing value in the calculation of related ratios. For urine protein, a value of "< 4.0" is handled as a missing value in the calculation of UPCR.

iii) Summary tables will be based on Gilead-calculated ratios.

iv) Listings will include both Gilead-calculated and Covance-calculated ratios

25) Combined category of UP and UPCR (Gilead computed)

a) First merge UP and UPCR based on the subject identifier and accession number (prior to any application of LOCF or BlOCF).

b) At each visit, use UP to select which pair of records should be used for the analysis. That is, once a UP record is selected for that visit, the UPCR with the same accession number will be selected.

c) The baseline value will be the last nonmissing value on or prior to the first dosing date of study drug. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosin

d) g of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the lowest severity (UPCR ≤ 200 mg/g) will be taken or if severity is also the same the later clinical visit will be taken.

e) The postbaseline record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected. If there are multiple records on the selected day, the worse severity (UPCR > 200 mg/g) will be taken or if severity is also the same the later clinical visit will be taken.

26) Graded Laboratory Abnormalities Summary

The following labels will be used for treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities summary tables and listings:

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Lymphocytes	Decrease	Lymphocytes (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	Amylase	Increase	Amylase (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatinine	Increase	Creatinine (Increased)
	GGT	Increase	GGT (Increased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Fasting)	Decrease	Serum Glucose (Fasting, Hypoglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Decrease	Serum Glucose (Nonfasting, Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Uric Acid	Decrease	Uric Acid (Hypouricemia)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Urinalysis	Urine Blood (Dipstick)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC (Quantitative)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*

* Due to the reflexive nature of the quantitative urine RBC test, results will be combined with the dipstick test of urine blood as described below. General rule is that urine RBC (Quantitative) should always be used first (if available), no matter it is collected at the same time of Urine Blood (Dipstick) or not. The combined Urine RBC (hematuria, Quantitative or Dipstick) toxicity grade will be used for "Maximum treatment emergent toxicity grade" summary.

Is Post-BL Urine RBC (Quant.) Result Available?	Is BL Urine RBC (Quant.) Result Available?	Is Post-BL Urine Blood (Dipstick) Result Available?	Is BL Urine Blood (Dipstick) Result Available?	How to Determine Treatment-Emergent Toxicity for "Urine RBC (Hematuria, Quantitative or Dipstick)"
Yes	Yes	-	-	Compare post-BL Urine RBC (Quant.) toxicity grade to BL Urine RBC (Quant.) toxicity grade. If post-BL toxicity is greater than BL toxicity, then treatment-emergent
Yes	No	-	-	Treatment-emergent. Use post-BL Urine RBC (Quant.) toxicity grade.
No	-	Yes	Yes	Compare post-BL Urine Blood (Dipstick) toxicity grade to BL Urine Blood (Dipstick) toxicity grade. If post-BL toxicity is greater than BL toxicity, then treatment-emergent
No	-	Yes	No	Treatment-emergent. Use post-BL Urine Blood (Dipstick) toxicity grade.
No	-	No	-	Do not count subject in the denominator for "Urine RBC (Hematuria, Quantitative or Dipstick)"

BL Baseline. Quant Quantitative. " " means any value can be present (or it can be missing), as it does not affect the classification

27) Toxicity Grades:

a) For toxicity grade summaries, include all post-baseline graded results up to 30 days after the last dose of study drug, not just those used in by-visit summaries.

b) For nonfasting glucose, fasting glucose, fasting total cholesterol, fasting triglycerides and fasting LDL grading, as specified in SAP Section 7.2.2.1, the treatment-emergent flag cannot be determined for approximately half of the subjects. As a result, these records will be excluded from the "Maximum Treatment-emergent Toxicity Grade" summary in the "Treatment-emergent Laboratory Abnormalities", Treatment-emergent Grade 2, 3 or 4 Laboratory Abnormalities" or "Treatment-emergent Grade 3 or 4 Laboratory Abnormalities" summary tables. In addition, fasting glucose and nonfasting glucose will be listed as two separate laboratory tests in the "Graded Laboratory Abnormalities" and "Grade 3 or 4 Laboratory Abnormalities" listings. Only a maximum postbaseline toxicity flag will be displayed and the treatment-emergent flag will not be displayed for these tests when the treatment-emergent flag cannot be determined.

c) Toxicity grades for CD4 will not be displayed in listings. CD4 is scheduled for collection following HIV infection and toxicity grades apply to HIV uninfected subjects.

28) Clarification for "Pharmacokinetic Blood Sampling Time Record" listing

a) A new variable "Sample age" will be added in this listing, defined as the duration in day between sample collection date and assay date, ie, sample age assay date sample collection date + 1.

b) SAMTIME (hours) sample collection time (xx:xx) - last dose time before sample collection (xx:xx).

28) PK parameters at the individual subject level should be displayed with the following reported number of decimal places:

- PK concentration data will be reported with 1 decimal place.

29) Concomitant nonstudy-drug ARV medications (ie, ARV medications other than study drug that are taken while receiving study drug) will be flagged in "Nonstudy-Drug Antiviral Medication" listing. The logic to define concomitant nonstudy-drug ARV is similar to concomitant non-ARV Medications (see details in Section 7.6.5)

30) Lipid modifying medication analyses:

a) Lipid modifying medication is defined to be the concomitant medication with ATC2 CMCLAS term "LIPID MODIFYING AGENTS" and CMDECOD contains wording of "STATIN" in the ADCM dataset.

b) Subjects who took lipid-modifying medications at study entry refer to the subjects who use of the lipid-modifying agents at study day 1 (ie, the first dose date). More specifically, subjects with "Lipid Modifying Agent Use at Study Entry" include those subjects in Safety Analysis Set with: 1) any selected CM record with the start date ≤ the first dose date, and 2) the end date of the selected CM record is ongoing or the end date of the selected CM record ≥ the first dose date.

c) Subjects who initiated lipid-modifying medications during the study include the subjects in the Safety Analysis Set who didn't take lipid-modifying medications at study entry and met the following criteria: 1) for subjects who permanently discontinued study drug with any selected CM record started after the first dose date and on and prior to the last dose date; 2) for subjects who are still on study drug with any selected CM records started after the first dose date.

d) For lipid-modifying medications with the start date completely unknown, we assume the start date is on or before the first dose date, lipid-modifying medication was considered as being taken at study entry if the end date is not prior to the first dose date (ie, the end date is on or after the first dose date, completely unknown, or ongoing).

e) Lipid modifying medications with the start date prior to the first dose date and the end date completely unknown were considered as being taken at study entry.

31) For figures, if at a visit where n (sample size) for any treatment group ≤ 5, data for that treatment group will not be displayed at the visit in figure (except the Kaplan-Meier figure), but all data will be included in the corresponding table summary.

32) Baseline HBV and HCV infection:

- The following table presents the HBV and HCV tests with all possible values. Values that have an asterisk after them denote a "positive" (or "quantifiable" for HBV DNA and HCV RNA) result while all others denote a "negative" result.

Label	LBTESTCD	LBTEST	Possible Values
HBsAg	CNT63	Hep B Surface Ag	"Positive"*, "Positive, Confirmed"*,"Negative"
HBsAb	CNT353	anti-Hep B Surface Ag2 Qual	"Positive"*, "Negative"
HBcAb	CNT68	Hepatitis B Core Total	"Positive"*, "Negative"
HBV DNA	GET1883	HBV DNA CAP/CTM 2.0-EDTA-CL	"No HBV DNA detected", "<20 IU/mL HBV DNA detected", ">170000000"*, *NUMERICAL VALUE**
HCVAb	CNT350	Hepatitis C Virus Antibody	"Positive"*, "Indeterminate", "Negative"
HCV RNA	GET1881	HCV RNA CAP/CTM 2.0EDTA-CL	"No HCV RNA detected", "<15 IU/mL HCV RNA detected", *NUMERICAL VALUE**

- For baseline infection, when considering the different laboratory tests, take the latest, non-missing record on or prior to the first dose date for each test (ie, HBsAg, HBsAb, HBcAb, and HBV DNA)

a) The baseline infection status will be one of the three values: Yes/No/Null

b) The following tables provide combinations of HBV and HCV tests and the corresponding baseline infection status

HBsAg	HBsAb	HBcAb	HBV DNA	Infection Status
Positive	-	-	-	Y
Negative	Positive	-	-	N
	Negative	Positive	Quantifiable	Y
			Not Quantifiable	N
			Missing	Null
		Negative	-	N
		Missing	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
	Missing	Positive	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
		Negative	-	N
		Missing	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
Missing	Positive	-	-	Null
	Negative	Positive	Quantifiable	Y
			Not Quantifiable	Null
			Missing	Null
		Negative	-	Null
		Missing	-	Null
	Missing	-	-	Null

HCVAb	HCV RNA	Infection Status
Positive	Quantifiable	Y
	Not Quantifiable	N
	Missing	Null
Negative	-	N
Missing	Quantifiable	Null
	Not Quantifiable	N
	Missing	Null

" " means any value can be present, as it does not affect the classification

33) For race, any black includes black and mixed races with any black ancestry (mixed black). Mixed black include Race "Other" when the Other Specify term includes 'BLACK' or 'AFR'. Race subgroup analyses (ie, black vs. nonblack) will exclude subjects with Race "Not Permitted."

34) CASI questionnaire dynamic questions

a) Screening CASI: Men Bottom [or Top] without condom last 90 days

- If QSTEST 'Men Bottom [or Top] without condom last 90 days' is missing, but 'Men Bottom [or Top] last 90 days' 0 then summarize 'Men Bottom [or Top] without condom last 90 days' 0

b) Baseline CASI: Men Bottom [or Top] wo Condom since Screening

- If QSTEST 'Men Bottom [or Top] wo Condom since Screening' is missing, but 'Men had Sex with since Screening' 0 then summarize 'Men Bottom [or Top] wo Condom since Screening' 0

c) Follow Up CASI:

- If QSTEST 'Men Bottom [or Top] wo Condom since last visit' is missing, but 'Men had Sex with since last study visit' 0 then summarize 'Men Bottom [or Top] wo Condom since Screening' 0

- If QSTEST 'Days Missed Tablets 7 Days BEFORE Sex [or AFTER Sex]' is missing, but 'Men Top without Condom since last visit' 0 and 'Men Bottom wo Condom since last visit' 0 then summarize 'Days Missed Tablets 7 Days BEFORE Sex [or AFTER Sex]' Not applicable

35) Identifying PEP versus PrEP from ARV medications:

Exclude any records that we are unable to classify as PEP or PrEP: (CMDECOD 'BLINDED INVESTIGATIONAL DRUG' or 'UNKNOWN DRUG') and CMTRT does not contain any of the following terms 'PREP' 'PRE EXPOSURE PROPHYLAXIS' 'PEP' 'POST EXPOSURE PROPHYLAXIS', 'CAB'

a) PrEP:

i) either cabotegravir (CMDECOD 'NON-GILEAD INVESTIGATIONAL DRUG' or CMDECOD 'BLINDED INVESTIGATIONAL DRUG') and CMTRT contains 'CAB'

ii) F/TDF or generic F/TDF medication for PrEP is defined as any treatment course that includes both FTC and TDF without any other 3rd ARV agents as follows:

(1) F/TDF: CMDECOD 'TRUVADA' or

(2) Generic F/TDF: overlapping medications of CMDECOD 'EMTRICITABINE' and CMDECOD 'TENOFOVIR DF' where the medication start and end dates overlap or

(3) Potential F/TDF for PrEP: CMDECOD (''BLINDED INVESTIGATIONAL DRUG or 'UNKNOWN DRUG') and (CMTRT includes 'PREP' or 'PRE EXPOSURE PROPHYLAXIS')

and

(4) where there are no other overlapping ARV medications (excluding cabotegravir or HIV vaccine)

At any time that the medication start and end dates of F/TDF (or generic F/TDF) does not overlap with any other medication start and end dates of another ARV agent (or overlaps by l day), that F/TDF (or generic F/TDF) record will be considered as treatment for PrEP.

Each ARV agent can be matched to only 1 F/TDF (or generic F/TDF) record, however, a single F/TDF (or generic F/TDF) record may be considered as taken both for PEP and PrEP if the F/TDF record start and/or end date extends past the other ARV agent start and/or end date.

If a partial month/year (or year only) medication end date and consecutive medication start date exactly match, these records will not be considered overlapping.

b) PEP:

i) Unknown or blinded medications for PEP: (CMDECOD 'BLINDED INVESTIGATIONAL DRUG' or 'UNKNOWN DRUG') and (CMTRT includes 'PEP' or 'POST EXPOSURE PROPHYLAXIS')

ii) Include other known ARVs (where CMDECOD not 'BLINDED INVESTIGATIONAL DRUG' or 'UNKNOWN DRUG') excluding the following:

(1) F/TDFa l

(2) generic F/TDF

(3) HIV vaccine

iii) For HIV infected subjects, excludes HIV treatments starting on or after the date of HIV diagnosis

At any time that the medication start and end dates of F/TDF (or generic F/TDF) overlaps with the medication start and end dates of another ARV agent (excluding cabotegravir or HIV vaccine) by more than 1 day, that F/TDF (or generic F/TDF) record will be considered as treatment for PEP.

Each ARV agent can be matched to only 1 F/TDF (or generic F/TDF) record.

If the medication start and end dates exactly match between both F/TDF (or generic F/TDF) and another ARV agent, the record will be considered as treatment for PEP, including when the exact match is based on partial medication start and/or end dates of month/year only, year only, completely unknown dates or end date ongoing.

36) For the follow up time of HIV infections while on-treatment,

a) if the start date of any non-study PrEP treatment that includes the period after permanent discontinuation of study drug is incomplete, such instances should be queried. If incomplete start dates remain after query, the first of the month should be used for the start date of the non-study PrEP medication when determining on-treatment HIV infection events or on-treatment follow-up time.

b) if any non-study F/TDF for PrEP treatment that includes the period after permanent discontinuation of study drug overlaps with a 3rd ARV agent, the start date of non-study PrEP treatment will be used unless the start date of the 3rd ARV agent and non-study F/TDF is the same in which case the end date + 1 day of the 3rd ARV agent will be used as the start date for non-study F/TDF for PrEP treatment. Incomplete start and end dates should be queried. If incomplete end dates of the 3rd agent remain after query, the last day of the month should be used for the start date of the non-study PrEP medication when determining on-treatment HIV infection events or on-treatment follow-up time.

37) Subjects who received HIV vaccine will be identified through the Medical History eCRF verbatim terms (MHTERM) or the Non-Study ARV Medication eCRF drug name (CMTRTOT) containing both of the terms ‘HIV’ and ‘vaccine’.

SAP GS-US-412-2055 EOBT Analysis

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	12-Dec-2019 17:20:05
PPD	Project Team Leader eSigned	13-Dec-2019 15:37:46