CLINICAL STUDY PROTOCOL

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	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	127728	
EudraCT Number:	2016-001399-31	
Indication:	Pre-Exposure Prophylaxis of HIV-1 Infection	
Protocol ID:	GS-US-412-2055	
Clinical Program Manager:	Name: Telephone: Fax:	PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax:	PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3: Amendment 4: Amendment 5: Amendment 6: Amendment 7:	07 April 2016 06 June 2016 15 July 2016 16 November 2016 06 April 2018 05 September 2018 10 November 2020 19 October 2021

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Gilead Sciences, Inc., and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Gilead Sciences, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

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
IND Number: **EudraCT Number:**	127728 2016-001399-31
Study Centers Planned:	Approximately 100 centers in North America and Europe
Objectives:	The primary objective of this study is: • To assess the rates of HIV-1 infection in men who have sex with men (MSM) and transgender women (TGW) who have sex with men who are administered daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) with a minimum follow up of 48 weeks and at least 50% of the participants 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 MSM and TGW who have sex with men who are administered daily F/TAF or F/TDF when all participants have 96 weeks of follow up after randomization • To compare the general safety between the treatments

	CCI [redacted]
Study Design:	Randomized, double-blind comparison of the safety and efficacy of F/TAF versus F/TDF administered orally once daily. All participants must meet eligibility criteria in order to receive treatment in the study. Once randomized to receive treatment in the study, all participants must return to the study center for required visits at Weeks 4, 12, and every 12 weeks thereafter. All participants will remain blinded to study drug for at least 96 weeks. The primary endpoint data will be collected and analyzed after all participants have a minimum follow up of 48 weeks and at least 50% of participants have 96 weeks of follow up after randomization. Once all participants have at least 96 weeks of follow up after randomization and upon notification by Gilead, all participants will return to the study center for an end of blinded treatment phase visit (may coincide with their next scheduled visit). Participants who are still on blinded study drug at the end of blinded treatment phase visit will be offered entry into the OL phase of the study. Participants who continue participation in the OL phase will be administered F/TAF once daily and will return to the study center for visits every 12 weeks. CCI [redacted] Participants who have discontinued study drug prior to the end of blinded treatment phase visit due to HIV infection will be eligible to continue participation in the OL phase, but will not be administered F/TAF once daily. From

	OL Week 48, participants who acquire HIV must complete the early study drug discontinuation (ESDD) visit and discontinue the study at the 30-Day Follow-up visit, 30 days after the last dose of study drug. Participants who have discontinued study drug for any other reason prior to the end of blinded treatment phase visit will not be eligible to participate in the OL Phase. CCI [redacted]
Number of Participants Planned:	5000
Target Population:	MSM and TGW (male at birth) who are at risk of HIV-1 infection through sexual exposure with other men
Duration of Treatment:	**Blinded Phase:** Participants will receive study drug for at least 96 weeks. After completing the Week 96 visit, all participants will continue to take their blinded study drug and attend visits every 12 weeks until the last participant reaches Week 96. All participants 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. CCI [redacted] **Open-Label Phase:** Participants will receive OL F/TAF for up to 96 weeks and will continue OL study visits every 12 weeks. From OL Week 48, participants who acquire HIV must complete the ESDD visit and discontinue the study at the 30-Day Follow-up visit 30 days after the last dose of study drug. **Open-Label Extension Phase:** CCI [redacted] Participants who have been diagnosed and confirmed as HIV positive during this phase must complete the ESDD visit and discontinue the study at the 30-Day Follow-up visit, 30 days after the last dose of study drug.

Diagnosis and Main Eligibility Criteria:	• HIV-1negative status • MSM or TGW (male at birth) who have at least one of the following: a) condomless anal intercourse with at least 2 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 • No suspected or known active, serious infection(s) • Estimated glomerular filtration rate ≥ 60 mL/min according to the Cockcroft-Gault formula • Adequate liver and hematologic function: • Aspartate aminotransferase (AST) and alanine aminotransferase (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, and hemoglobin ≥ 10 g/dL • Have not received investigational agents for the treatment or prevention of HIV-1 infection in the 30 days prior to screening • No evidence of acute viral hepatitis A, B or C, and no evidence of chronic hepatitis B virus infection. Participants found to be susceptible to hepatitis B virus (HBV) infection should be referred for HBV vaccination. Participants found to be positive for hepatitis C virus (HCV) must not have active infection or must have completed treatment and achieved a sustained virologic response • No history of osteoporosis or bone fragility fractures
Study Procedures/ Frequency:	**Screening Visit** Upon providing written informed consent, participants will be evaluated for eligibility at the screening visit, including medical history review, concomitant medication review, complete physical examination including height, weight, and vital signs, sexually transmitted infection (STI) testing for gonorrhea, chlamydia, and syphilis, fourth generation rapid HIV-1 antibody (Ab)/antigen (Ag) or third generation rapid HIV-1 Ab test, HIV Ab/Ag testing, HIV-1 RNA testing if applicable, Hepatitis B testing, Hepatitis C testing, clinical laboratory assessments for blood and urine samples,

	computer-assisted self-interview (CASI) for: recent sexual risk events; interest in using PrEP; self-identification of transgender status; education and employment history; and use of tobacco and recreational drugs, and risk reduction counseling including provision of condoms. Prior to the Day 1 visit and randomization, the investigator will review the screening assessments to confirm eligibility. The Day 1 visit must occur within 30 days after the screening visit. **Blinded Treatment Phase** During the blinded treatment phase, participants will be seen at the study center for visits at Day 1, Weeks 4, 12, 24, and every 12 weeks thereafter until the end of blinded treatment phase visit. At the Day 1 visit, participants will be assessed with fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test, HIV-1 RNA if applicable, adverse event (AE) and concomitant medication review, targeted physical examination and vital signs if applicable, CASI, and adherence and risk reduction counseling including provision of condoms. CCI [redacted]. At all other study visits during the blinded treatment phase, participants will be assessed with targeted physical examination (complete physical examination at Week 48 and 96), AE and concomitant medication review, vital signs if clinically indicated, weight, STI testing for gonorrhea, chlamydia, and syphilis, fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test, HIV Ag/Ab testing, HIV-1 RNA testing if applicable, Hepatitis B testing (every 24 weeks), Hepatitis C testing (every 48 weeks), clinical laboratory assessments for blood and urine samples, plasma storage sample collection, CCI [redacted] CCI [redacted]. If the participant discontinues study drug prior to the end of blinded treatment phase visit, the participant will be asked to return to the study center within 72 hours of stopping study drug for the ESDD visit. The participant will be asked to continue attending the scheduled study visits through the end of blinded treatment phase visit of the study. CCI [redacted]. Participants who are still on study drug at the end of blinded treatment phase visit will be offered entry into the OL phase and OL

	extension phase of the study. Participants who have discontinued study drug prior to the end of blinded treatment phase visit due to HIV infection will be eligible to continue participation in the OL phase up to OL Week 48, but will not be administered F/TAF once daily. **Open-Label Phase** During the OL phase, participants will be seen at the study center for visits every 12 weeks up to OL Week 96. At all study visits during the OL phase, participants will be assessed with targeted physical examination (complete physical examination at OL Week 48), AE and concomitant medication review, vital signs if clinically indicated, weight, STI testing for gonorrhea, chlamydia, and syphilis, fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test, HIV Ab/Ag testing, HIV-1 RNA testing if applicable, Hepatitis B testing (every 24 weeks), Hepatitis C testing (every 48 weeks), clinical laboratory assessments for blood and urine samples, plasma storage sample collection, [redacted] Throughout the study, participants may be asked to provide daily information on adherence and sexual risk events through the use of a diary. Participants may also receive periodic contacts to remind them to take their study drug and to provide any additional support needed. **Open-Label Extension Phase**
	During the OL extension phase, participants will be seen at the study center for visits every 12 weeks from OL Week 96 up to OL Week 408. At all study visits during the OL extension phase, participants will be assessed with targeted physical examination (every 24 weeks), AE and concomitant medication review, vital signs (every 24 weeks), weight (every 24 weeks), STI testing for gonorrhea, chlamydia, and syphilis, at a minimum fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test, HIV Ab/Ag testing, HIV-1 RNA testing if applicable, Hepatitis B testing (every 48 weeks), Hepatitis C testing (every 48 weeks), clinical laboratory assessments for blood samples, DBS collection and risk reduction counseling including provision of condoms.
Test Product, Dose, and Mode of Administration:	**Blinded Phase:** F/TAF fixed-dose combination (FDC) (200 mg emtricitabine/25 mg tenofovir alafenamide), administered orally once daily. **Open-Label and Open-Label Extension Phase:**

	F/TAF FDC (200 mg emtricitabine/25 mg tenofovir alafenamide), administered orally once daily.
Reference Product, Dose, and Mode of Administration:	**Blinded Phase:** F/TDF FDC (200 mg emtricitabine/300 mg tenofovir disoproxil fumarate), administered orally once daily.
Criteria for Evaluation:	
Safety:	• Adverse events • Physical examinations, vital signs • Clinical laboratory tests of blood and urine • CCI [redacted] • STI testing • Adherence measures including tablet collection, responses to adherence questions as part of the CASI, and FTC and/or TFV levels in the plasma or DBS
Efficacy:	Incidence of HIV-1 infection 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 Ag/Ab or Ab test, confirmed by the reactive HIV-1/HIV-2 differentiation assay), excluding HIV vaccinated participants, or 2) Virologic evidence of HIV-1 infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV-1 RNA test), or 3) Evidence of acute HIV-1 infection (reactive p24 Ag or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Ab results) Please refer to Appendix 7 for more details.
CCI [redacted]	[redacted] CCI
Risk Behavior Assessment:	Computer-Assisted Self-Interview (CASI) sexual risk event evaluation
Statistical Methods:	The primary endpoint will be the incidence of HIV-1 infection (as defined above) per 100 person years (PY). The primary analysis will occur when all participants have a minimum of 48 weeks of follow up and at least 50% of the participants have at least 96 weeks of follow up after randomization.

	The primary analysis will consist of a non-inferiority evaluation of F/TAF versus F/TDF, with respect to the HIV-1 infection rate in PY as determined by rate ratios. It will be concluded that F/TAF is non-inferior to F/TDF if the upper bound of the 95% CI of the ratio between the two arms (F/TAF over F/TDF) is less than 1.62. The 95% CI will be constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the covariate. A sample size of 2500 in each arm provides at least 82% power to show F/TAF is non-inferior to F/TDF with respect to the HIV-1 infection rate, and assumes an HIV-1 infection rate of 1.44 per 100 PY in the F/TAF and F/TDF treatment arms, a 2-sided Type 1 error rate of 5%, and an average follow up of 2 years (ie, last participant has a minimum of 48 weeks of follow up and at least 50% of the participants have at least 96 weeks of follow up after randomization). An independent data monitoring committee (IDMC) will be convened to primarily evaluate the safety of the treatments in this population. There are no prior plans to stop for efficacy or futility with formal boundaries. At a minimum, the IDMC will include 2 clinicians (including a chairperson), a biostatistician, a prevention expert, and a community member. The initial evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 24 (or prematurely discontinued from the study drug) or (2) after 50 HIV-1 infections have been reported, whichever occurs earlier. The second evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 48 (or prematurely discontinued from the study drug) or (2) after 100 HIV-1 infections have been reported, whichever occurs earlier. The third evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 72 (or prematurely discontinued from the study drug) or (2) after 150 HIV-1 infections have been reported, whichever occurs earlier.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab	antibody
AE	adverse event
Ag	antigen
AK	adenylate kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BMD	bone mineral density
BUN	blood urea nitrogen
CASI	computer-assisted self-interview
CBC	complete blood count
CD4	cluster determinant 4
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
C_{trough}	concentration at the end of the dosing interval
CYP	cytochrome P450
DBS	dried blood spot
DNA	deoxyribonucleic acid
DXA	dual-energy X-ray absorptiometry
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESDD	early study drug discontinuation

EU	European Union
F	emtricitabine (Emtriva®)
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
F/TDF	emtricitabine/tenofovir disoproxil fumarate
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
FTC-TP	emtricitabine 5′-triphosphate
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma glutamyltransferase
GI	gastrointestinal
Gilead	Gilead Sciences
GLPS	Global Patient Safety
HBcAb	hepatitis B virus core antibody
HBsAb	hepatitis B virus surface antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IDMC	independent data monitoring committee
IEC	independent ethics committee
IMP	Investigational Medicinal Product
IRB	institutional review board
IV	intravenous
IXRS	interactive voice/web response system
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LOCF	last observation carried forward
MSM	men who have sex with men
NA	not applicable

NOAEL	no observed adverse effect level
NRTIs	nucleotide reverse transcriptase inhibitors
OL	open label
PBMC	peripheral blood mononuclear cell
PBO	placebo
PCR	polymerase chain reaction
PD	pharmacodynamics
PEP	postexposure prophylaxis
PI	principal investigator
PK	pharmacokinetics
PP	Per Protocol
PrEP	pre-exposure prophylaxis
PRT	proximal renal tubulopathy
PT	Preferred Term
PY	person years
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
RBC/HPF	red blood cells per high power field
RBP	retinol-binding protein
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
SDV	source data verification
SHIV	simian/human immunodeficiency virus
SOC	System Organ Class
SOP	standard operating procedure
STB	Stribild®
STI	sexually transmitted infection
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TGW	transgender women
ULN	upper limit of normal
UNAIDS	United Nations Programme on HIV/AIDS
UP	urine protein
UPCR	urine protein to creatinine ratio

URAI	unprotected receptive anal intercourse
US	United States

1. INTRODUCTION

1.1. Background

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that there were 1.5 million new HIV-1 infections in 2020 despite widespread knowledge of the protective effects of abstinence, monogamy, and condoms in preventing new HIV-1 infections {UNAIDS, 2020}. The principal interventions used to prevent HIV transmission have been voluntary testing and counseling and the promotion of condoms. The effectiveness of these interventions has been variable {Coates 2000, Higgins 1991, Wolitski 1997} and the prevalence of HIV-1 infection remains high even in settings with 100% condom promotion policies {Lertpiriyasuwat 2003}. Additionally, new HIV-1 infections in the United States (US) have been consistently stable at about 50,000 per year, and 70% of these are in men who have sex with men (MSM), with or without concurrent injection drug use {Centers for Disease Control (CDC) 2015}; in fact, the proportion of new infections due to male-to-male transmission increased from 2010-2014. Although intense research has been conducted to develop a conventional vaccine against HIV-1 infection, these efforts have failed to produce a viable option. Thus, an important medical need exists for a novel approach to augment HIV-1 prevention services and reduce the spread of HIV-1 infection.

Pre-exposure prophylaxis strategies have been used to prevent transmission of infectious diseases such as malaria and HIV-1. Evidence supporting the efficacy of prophylaxis with antiretroviral (ARV) therapy (ART) in decreasing HIV-1 seroconversion can be found in experience with postexposure prophylaxis (PEP) in animal models {Tsai 1995, Van Rompay 2000, Van Rompay 2001} and in other clinical settings such as with occupational exposure with healthcare workers or with maternal-to-child transmission {Gerberding 1993}.

Truvada®, a fixed-dose combination (FDC) of emtricitabine (F, FTC) and tenofovir disoproxil fumarate (TDF), was first granted marketing approval by the US Food and Drug Administration (FDA) for use in combination with other agents for the treatment of HIV-1 infection in adults on 02 August 2004. On 16 July 2012, a supplemental New Drug Application (sNDA) 021752/S-030 was approved to expand the use of Truvada in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. While TDF is an effective drug used broadly (as part of multiple combination regimens) in both the treatment and prevention of HIV-1 infection, nephrotoxicity has been reported with the use of TDF and manifests as increased creatinine, increased protein loss (particularly tubular), and occasional cases of proximal renal tubulopathy (PRT) (including Fanconi Syndrome). These TDF-associated renal risks necessitate increased renal monitoring, placing burden on the patient and healthcare provider. In addition, early onset bone demineralization in adults has also been reported with use of TDF, specifically reductions in bone mineral density (BMD); the decreases in BMD with TDF are larger than those seen with other nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) {Gilead Sciences International Limited 2016, VIREAD® 2016}.

Gilead has coformulated FTC with tenofovir alafenamide (TAF) into a FDC for use once daily in combination with other ARV agents for the treatment of HIV-1 in adults and pediatric patients 12 years of age and older. Tenofovir alafenamide is a new prodrug of the N(t)RTI tenofovir (TFV) that is more stable in plasma than TDF. TAF has pharmacokinetic (PK) properties that distinguish it from TDF, with clinically important consequences. TAF 25 mg achieves > 4-fold higher intracellular levels of the pharmacologically active phosphorylated metabolite tenofovir diphosphate (TFV-DP) in peripheral blood mononuclear cells (PBMCs) and ~90% lower circulating levels of TFV relative to TDF (300 mg). This marked reduction in circulating TFV is associated with smaller changes in clinical markers of renal function (eg, proteinuria) and in BMD that are consistent with those seen in participants receiving non-TDF containing regimens.

Key Phase 3 clinical data from the Genvoya® clinical program demonstrates that F/TAF-containing regimens significantly improve bone safety profile as compared with TDF-based regimens, specifically, significantly less reduction in BMD at both the hip and spine for ART-naive participants compared to Stribild® (STB), and significant improvements in BMD for participants who switched from a TDF-based regimen to Genvoya. Additionally the data demonstrates that F/TAF-containing regimens significantly improve renal safety profile as compared with TDF-based regimens, specifically, significantly less change in serum creatinine, proteinuria, and specific renal tubular proteinuria for ART-naive participants compared with STB; and a significant reduction in serum creatinine levels and significant improvements in renal tubular protein parameters for participants who switched from a TDF-based regimen to Genvoya.

F/TAF has favorable characteristics that make it suitable for evaluation as chemoprophylaxis, including higher PBMC intracellular concentrations of the pharmacologically active metabolite TFV-DP than TDF-based regimens with potent antiviral effects, a long intracellular half-life of more than 24 hours for TFV-DP, convenient once-daily oral dosing, a favorable tolerability profile, and infrequent selection of drug resistance mutations. Efficacy of F/TAF for chemoprophylaxis has been demonstrated by preventing simian/human immunodeficiency virus (SHIV) infection in a rhesus monkey model (see Section 1.2.2).

Use of F/TAF is less likely to impact bone mineralization in younger adults 18-25 and less likely to impact kidney function in older adults who are at increased risk of chronic kidney disease. Once commercially available, the use of F/TAF for PrEP in uninfected individuals at high risk of acquiring HIV infection may provide an effective prevention regimen with a significantly improved renal and bone safety profile relative to Truvada.

1.2. Tenofovir Alafenamide (TAF, GS-7340)

1.2.1. General Information

Tenofovir alafenamide (GS-7340, TAF, or L-Alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)1-methylethoxy]methyl]/phenoxyphosphinyl]-, 1-methylethyl ester) is an oral prodrug of TFV, a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, TFV-DP, a competitive inhibitor of HIV-1 reverse transcriptase that terminates the elongation of the viral DNA chain. In the development of TAF, 3 forms of the drug substance have been used in various studies: GS-7340, synonym for GS-7340 as the free base; GS-7340-02, synonym for TAF monofumarate (1:1); and GS-7340-03

as the hemifumarate (2:1). GS-7340-03, also known as TAF fumarate, is considered comparable based on physical/chemical properties to GS-7340-02 that has been used in previous studies and a number of ongoing studies. GS-7340-03 was also used in the Phase 2 Study GS-US-292-0102 and is being used in several ongoing Phase 3 studies (for example: GS-US-292-0104 and GS-US-292-0111). GS-7340-03 and GS-7340-02 exist as the free base, TAF (GS-7340), in blood and biological fluids.

For further information on F/TAF, refer to the current investigator's brochure (IB) for F/TAF.

1.2.2. Nonclinical Studies of F/TAF for PrEP

Nonclinical pharmacology studies in rhesus macaques show that orally administered F/TAF, at doses resulting in PBMC exposures that are consistent with those achieved in humans administered a dose of F/TAF 200/25 mg, effectively prevents SHIV infection.

Using a design similar to a previous Centers for Disease Control and Prevention (CDC) study of F/TDF in rhesus macaques {Garcia-Lerma 2010}, researchers at the CDC demonstrated that oral administration of F/TAF in rhesus macaques prevents infection with a chimeric SHIV (PC-412-2001). The dose of TAF selected for administration in the SHIV viral challenge study was based on an initial PK study in macaques wherein a TAF dose of 1.5 mg/kg was shown to result in intracellular concentrations of the active moiety TFV-DP in PBMCs consistent with those seen with use of a TAF 25 mg dose in humans (see PK section below). FTC was dosed at 20 mg/kg based on a similar rationale, and consistent with the previous study with F/TAF in macaques. In the SHIV viral challenge study, 12 healthy rhesus macaques were administered weekly inoculations of intrarectal SHIV. Twenty-four hours before each rectal inoculation and 2 hours after each rectal inoculation, one group of 6 animals was administered 20 mg/kg FTC and 1.5 mg/kg TAF by oral gavage and one group of 6 animals was administered placebo (saline control) by oral gavage. SHIV challenges and paired gavages were administered once a week for up to 19 weeks (schematic of the study design is provided in Figure 1-1). All 6/6 macaques given placebo (saline control) became infected with SHIV, while 0/6 macaques given F/TAF became infected with SHIV (results shown in Figure 1-2).

Figure 1-1. Design of Study PC-412-2001 of F/TAF for PrEP in Rhesus Macaques

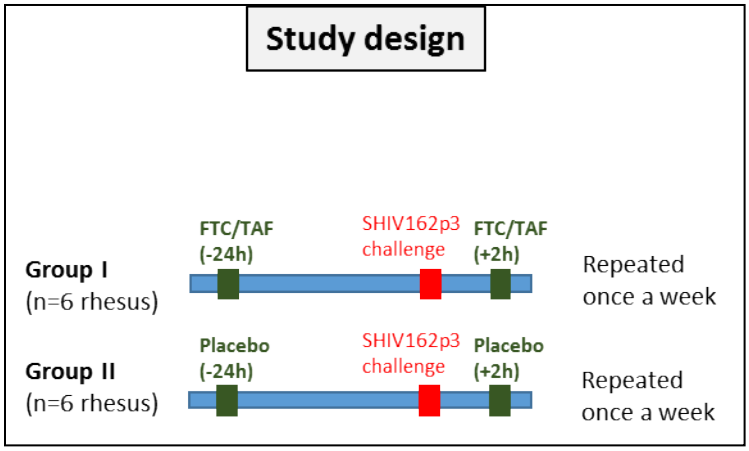
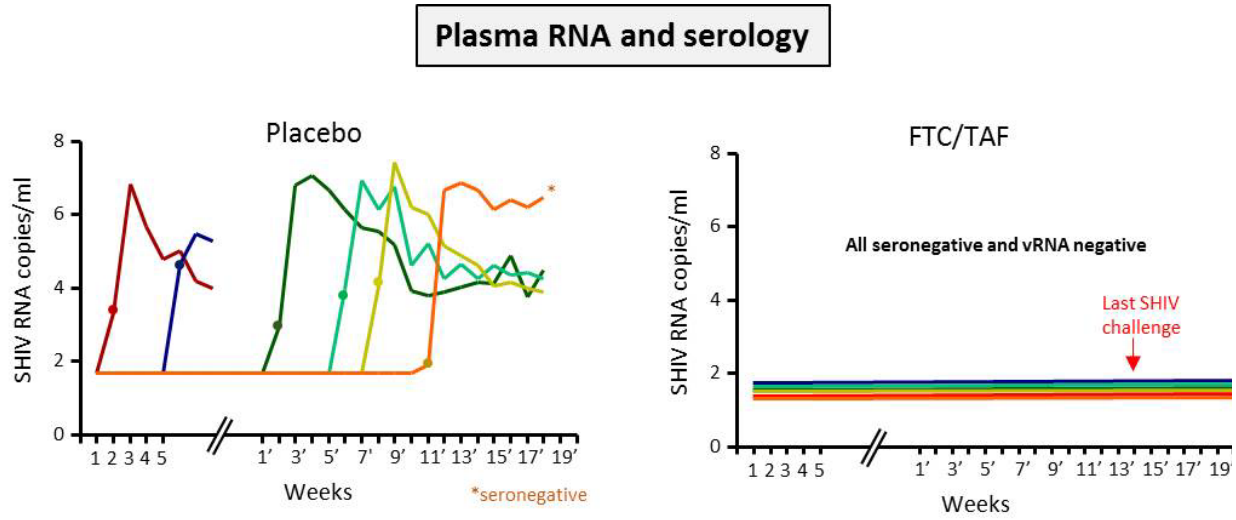


Figure 1-2. Plasma RNA and Serology Results from Study PC-412-2001 of F/TAF for PrEP in Rhesus Macaques



Note: Each colored line represents an individual rhesus monkey. The Weeks 1-5 represent viral challenges with the initial viral stock. Weeks 1'-19' represent viral challenges with a second viral stock with higher infectivity.

The dose of TAF used in Study PC-412-2001 was chosen to target the PBMC exposure range observed in humans following administration of TAF 25 mg. While the definitive correlate of protection against mucosal viral exposure is not established, intracellular levels of TFV-DP have been consistently associated with both virologic suppression and with prophylaxis across a variety of human and animal studies {Abdool Karim 2010, Anderson 2012, Baeten 2012, Castillo-Mancilla 2013, Garcia-Lerma 2008, Grant 2010, Van Rompay 2012, Van Rompay 2001}.

The results of Study PC-412-2001 in rhesus macaques are consistent with the previously published CDC study of FTC and TDF conducted in the same nonhuman primate model {Garcia-Lerma 2010}. In the prior SHIV viral challenge study, rhesus macaques were inoculated with SHIV once a week for 14 weeks via intrarectal administration. Various dosing regimens using orally administered 20 mg/kg FTC and 22 mg/kg TDF (given 1, 3, or 7 days before exposure followed by a second dose 2 hours after exposure) were evaluated. In that study, 5 of 6 animals given oral F/TDF at 24 hours prior to SHIV inoculation and 2 hours after SHIV inoculation at doses equivalent to those administered to humans for treatment remained seronegative through 14 inoculation challenges of rectally administered SHIV. Protection against SHIV in rhesus macaques subject to rectal challenge has also been observed following daily subcutaneous administration of 20 mg/kg FTC and 22 mg/kg TFV, suggesting that local concentrations possible in the gastrointestinal tract following oral administration are not required for protection and that systemic loading of HIV-target cells (ie PBMCs) drives efficacy {Garcia-Lerma 2008}.

1.2.3. Preclinical Pharmacology and Toxicology

1.2.3.1. Primary Pharmacodynamics

TAF is metabolized to TFV, a nucleotide analog (ie, a nucleoside monophosphate analog) which is not dependent on an intracellular nucleoside kinase activity for the first step in the conversion to the active metabolite, TFV-DP. The cellular enzymes responsible for TFV metabolism to the active diphosphorylated form are adenylate kinase (AK) {Tsai 1995} and nucleotide diphosphate kinase, which are highly active and ubiquitous. AK exists as multiple isozymes (AK1 to AK4), with the phosphorylation of TFV mediated most efficiently by AK2.

The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV. Metabolism of TAF was also studied in different human blood lymphocyte subpopulations, cluster of determinant 4+ (CD4+) and cluster determinant 8+ (CD8+) T-cells, NK cells, B-cells and macrophages/monocytes. TAF is metabolized inside host cells to the active metabolite TFV-DP. Concentration of the active metabolite TFV-DP was substantial in all cell populations.

1.2.3.2. Safety Pharmacology

TAF monofumarate (GS-7430-02) has been evaluated to determine potential effects on the central nervous system (R990188), renal system (R990186), cardiovascular (D2000006) and gastrointestinal systems (R990187). Single doses did not induce pharmacologic effects on the central nervous system of the rat (1000 mg/kg), the renal system of the rat (1000 mg/kg), or the cardiovascular system of the dog (100 mg/kg). TAF monofumarate (at 1000 mg/kg reduced distal transit and increased stomach weights starting 2 hours postdosing with reversibility beginning by 6 hours after dosing. The no observed effect level (NOEL) for gastrointestinal motility was 100 mg/kg. The half-maximal inhibitory concentration (IC_{50}) for the inhibitory effect of TAF fumarate (GS-7340-03) on human ether-a-go-go-related gene (hERG) potassium current was estimated to be greater than 10 μM.

1.2.4. Nonclinical Pharmacokinetics

All nonclinical PK experiments in this section were performed using TAF monofumarate (GS-7340-02), and all study data described in this section reflect the dosage of the monofumarate. For reference, 100 mg of TAF monofumarate is equivalent to 80 mg of the GS-7340 free base (TAF).

Plasma PK of the intact prodrug, TAF, following oral administration of GS-7340-02 in dogs and monkeys demonstrated rapid absorption with peak plasma concentrations between 0.25 and 0.5 hours.

Peak TFV plasma concentrations occurred following TAF absorption, with TFV T_{max} values between 0.25 to 1.7 hours in rats, dogs, and monkeys. TFV plasma concentrations declined with a terminal half-life of 11.2 to 16.4 hours in rats (fasted), > 24 hours in dogs (fasted) and 8.1 to 12.5 hours in rhesus monkeys.

The tissue distribution and recovery of [^{14}C] radiolabeled GS-7340-02 was examined in beagle dogs. Radioactivity was detected in all tissues except brain, with the majority present in the contents of the gastrointestinal tract, liver, kidney, and large intestine. Tissue concentrations were the highest in kidney, PBMCs, liver, large intestine, and bile. Significant concentrations of TFV-related radioactive material were observed in lymph nodes suggesting that TAF may be selectively cleaved to tenofovir in the cells of the lymphoreticular system.

The primary route of elimination of tenofovir is renal excretion of unchanged drug based on IV studies of tenofovir. Following oral administration of GS-7340-02, approximately 15% of a radiolabeled dose is recovered in dog urine in 24 hours. Tenofovir was the major species present in the urine (90%), with about 3.4% of TAF also present. Biliary excretion of tenofovir in dogs and fecal elimination of tenofovir in rats and dogs are negligible.

Tenofovir was the only species found in the intestinal contents and feces. In human systems, TAF is metabolized by hydrolytic cleavage and, to a lesser extent, by cytochrome P450 (CYP)3A4 catalyzed oxidation (AD-120-2004). As a result of the limited metabolism of TAF by CYP3A4 inhibition or induction of this enzyme should have little consequence on TAF exposure in vivo. TAF has limited potential to alter CYP enzyme activity through inhibition and does not inhibit uridine glucuronosyltransferase (UGT)1A1 function. In addition, TAF is not an activator of either the aryl hydrocarbon receptor (AhR) or human pregnane-X-receptor (PXR). These features combined with the relatively low plasma exposures of TAF in humans suggest that the potential of TAF to cause or be affected by clinically relevant drug-drug interactions is very low.

1.2.5. Nonclinical Toxicology

TAF monofumarate (GS-7340-02) was evaluated in mice, rats, dogs, and monkeys for treatment periods up to 9-months and was negative in genetic toxicology studies.

In chronic studies in rats, bone (atrophy of metaphyseal cancellous bone) and kidneys (karyomegaly) were the primary target organs after 26 weeks of treatment. GS-7340-02 also appeared to increase biochemical markers of bone turnover and decrease serum 1,25-dihydroxy- and 25-hydroxyvitamin D3 at doses of 25 mg/kg/day and above. In chronic studies in dogs after 9 months of treatment with GS-7340-02, the primary target organs were kidney and bone. This chronic toxicity study of TAF in beagle dogs given 2 mg/kg/day, 6 mg/kg/day or 12-18 mg/kg/day for 9 months found non-specific mononuclear cell infiltrates seen on histopathology in the lungs, spleen and posterior uvea (eye) of animals in the 12-18 mg/kg group. This group of animals experienced generalized debility at the 18 mg/kg/day dose, so the dose was decreased after Week 6. The histopathologic changes were felt to be due to the overall condition of the animals and not specific TAF-related toxicity. There were no findings in the eyes of dogs treated with lower doses (2 mg/kg and 6 mg/kg), and it was concluded that the no observed adverse effect level (NOAEL) in beagle dogs was 2 mg/kg/day.

TAF monofumarate had no discernible electrocardiograph effect at the low dose of 2 mg/kg/day and slightly prolong PR intervals at 6 and 12-18 mg/kg/day. Additionally, at Week 39, TAF monofumarate appeared to reversibly reduce heart rate with an associated mild QT prolongation. At Week 39, decreases in serum triiodothyronine (T3) were noted for animals receiving 18/12 mg/kg/day but was reversible at the 3-month recovery period. Minor hematological and biochemistry parameters changes were observed but remained within normal historical ranges with the following exceptions: aspartate aminotransferase (AST) (~100% increase) and total bilirubin (~40% increase). There were no clear treatment-related effects observed in monkeys following 28 days of treatment including no changes in mitochondrial function.

The data from the 6-month rat study determined a NOAEL of 25 mg/kg/day (tenofovir AUC = 3758 ng•h/mL); the 9-month dog study defined a NOAEL of 2 mg/kg/day (tenofovir AUC = 1180 ng•h/mL), and the 28-day nonhuman primate study defined a NOAEL of 30 mg/kg/day (tenofovir AUC = 5870 ng•h/mL). In conjunction with the nonclinical data with TDF and the clinical experience with TDF and TAF, these toxicology studies support studies in humans of doses up to 150 mg/day (120 mg free base, the highest anticipated human dose) for chronic treatment.

At the time of the rodent toxicity studies, the bioassay could not detect plasma TAF, possibly due to instability in the matrix.

Because of the lack of exposure to the prodrug in mice and rats and achievable tenofovir exposures less than previously tested in chronic and carcinogenicity studies with TDF, carcinogenicity studies in mice and rats with TAF are not required per agreement with the FDA.

Also, TAF does not need to be evaluated in perinatal-postnatal reproductive toxicology studies per agreement with the FDA. Reproductive tissues were examined in repeat-dose toxicology studies in the rat, dog, and monkey. There were no clearly treatment-related histologic alterations or changes in organ weights in the rat and the dog following chronic daily dosing, or in the monkey.

The TAF fumarate (GS-7340-03) oral rat fertility study is ongoing (Report No. TX-120-2012, report in progress).

1.2.6. Clinical Trials of Single Agent Tenofovir Alafenamide (TAF, GS-7340) or Fixed-Dose Combination Emtricitabine/Tenofovir Alafenamide (F/TAF)

Clinical trials entailing the use of tenofovir alafenamide include:

- **GS-US-120-1101**, a Phase 1/2 study of the pharmacokinetics and antiviral activity of GS-7340 (50 mg and 150 mg) in HIV-infected participants (completed)

- **GS-US-120-0104**, a Phase 1b study of the pharmacokinetics and antiviral activity of GS-7340 (8 mg, 25 mg, 40 mg) in HIV-infected participants (completed)

- **GS-US-120-0107**, a Phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of GS-7340 on the QT/QTc interval in healthy participants (completed)

- **GS-US-120-0108**, a Phase 1, open-label, parallel-design study to evaluate the pharmacokinetics of GS-7340 in participants with severe renal impairment (completed)

- **GS-US-120-0109**, a Phase 1 study to evaluate the pharmacokinetics, metabolism and excretion of GS-7340 (completed)

- **GS-US-120-0114**, a Phase 1, open-label, parallel-group, single-dose study to evaluate the pharmacokinetics of tenofovir alafenamide in participants with normal and impaired hepatic function (completed)

- **GS-US-120-0117**, a Phase 1 single-dose study evaluating the pharmacokinetic drug interaction potential between rilpivirine and tenofovir alafenamide (completed)

- **GS-US-120-0118**, a pharmacokinetic study evaluating the drug interaction potential of tenofovir alafenamide with a boosted protease inhibitor or unboosted integrase inhibitor in healthy participants (completed)

- **GS-US-311-0101**, a Phase 1 healthy volunteer study evaluating the drug interaction potential between once-daily FTC/GS-7340 fixed-dose combination and efavirenz or cobicistat-boosted darunavir (completed)

- **GS-US-311-1088**, a Phase 1, Relative Bioavailability Study of Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet to evaluate the formulation performance of FTC and TAF fixed dose combination tablets relative to co-administration of individual agents (completed).

The first proof-of-concept study, GS-US-120-1101, as well as GS-US-120-0104 and GS-US-292-0101 were performed using TAF monofumarate (GS-7340-02). All subsequent studies were performed using TAF fumarate (GS-7340-03), with the exception of GS-US-311-0101 Cohort 4, which used the monofumarate (GS-7340-02) for the GS-7340 single agent 8-mg tablet.

GS-US-120-1101 was a Phase 1/2 randomized, double-blind, active-controlled, dose escalation study of the safety, tolerance, PK, and antiviral activity of TAF in ARV-naive patients who were chronically infected with HIV-1. The participants were randomized to receive 14 days of monotherapy, fasting, with TAF monofumarate 50 mg once daily, 150 mg once daily, or TDF 300 mg once daily (n = 10 per group). TAF was rapidly absorbed into the systemic circulation, and following attainment of C_{max}, was eliminated rapidly with a short plasma half-life (20-40 minutes). Compared with TDF, TAF monofumarate 50 mg provided a ~16-fold lower tenofovir C_{max} (207 ng/mL vs 13 ng/mL), about two-fold longer elimination half-life (26 hours vs 48 hours) and lower overall systemic tenofovir exposure (AUC_{inf}: 1814 ng•h/mL vs 383 ng•h/mL). TAF monofumarate 150 mg provided lower C_{max} (42 ng/mL), but comparable

AUC_{inf}: (1740 ng•h/mL) as TDF. In PBMCs, tenofovir was detectable earlier, more frequently, and in higher concentrations following dosing of TAF monofumarate. The intracellular delivery of tenofovir is approximately 30-fold greater for TAF monofumarate versus TDF. The decrease from baseline to Day 14 in plasma HIV-RNA levels was greater for groups treated with TAF monofumarate 50 mg ($p = 0.0257$) or 150 mg ($p = 0.0010$) than the group that received TDF 300 mg. The median changes from baseline in plasma HIV-1 RNA after 14 days of monotherapy were −0.96 $\log_{10}$ copies/mL for TDF 300 mg, −1.65 $\log_{10}$ copies/mL for TAF monofumarate 50 mg, and −1.68 for TAF monofumarate 150 mg.

A second proof-of-concept study, GS-US-120-0104, evaluated monotherapy, with 3 lower doses of TAF or TDF 300 mg, or placebo, administered in a fasted state for 10 days. Potent antiviral activity was achieved in treatment-naive HIV-1 infected patients, with mean (± SD) change from baseline in HIV-1 RNA of −0.98 ± 0.46, −1.50 ± 0.41, −1.74 ± 0.19, and −0.81 ± 0.58 log10 copies/mL at 8 mg, 25 mg, 40 mg dose of TAF, and TDF 300 mg, respectively. Mean viral load declines for both the 25 mg and 40 mg doses were statistically greater than the 8-mg dose. TAF exposure (AUC) was best associated with antiviral activity despite its short plasma half-life (~30 min). TFV AUC were 97%, 87%, and 80% lower at 8 mg, 25 mg, and 40 mg TAF compared to TDF administration. When compared with 40 mg and historical 120 mg data, 25 mg TAF provides near maximal activity (predicted to be ~ −1.7 to1.8 log10 c/mL). From this PK-pharmacodynamic (PD) analysis, a target dose of 20-25 mg TAF monotherapy is expected to provide near maximal activity and ~90% reduction in circulating TFV.

Study GS-US-120-0107 is a Phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of TAF on the QT/QTc interval in healthy participants. This was a negative thorough QTc study. No effect of TAF was observed on the QTcF interval (ie, no QTc interval prolongation > 10 msec at any time point postdose and assay sensitivity was confirmed via the positive control [moxifloxacin]). As such, these findings satisfy the guidelines set forth in the International Council for Harmonisation (ICH) E14 guidance and support the conclusion that there is no significant effect of TAF on the QT/QTc interval.

Study GS-US-120-0108 was a Phase 1, open-label (OL), parallel-design study to evaluate the PK of TAF in participants with severe renal impairment. TAF was well tolerated in the study. Patients with severe renal impairment had < 2-fold higher TAF and 5-6 fold higher TFV systemic exposures as assessed by AUC relative to participants with normal renal function. TFV exposures in participants with severe renal impairment are comparable to those with normal renal function receiving 300 mg TDF. Given the extensive safety data available for TDF at a dose of 300 mg, TFV exposures in severely renally impaired participants similar to those associated with TDF 300 mg are deemed appropriate for further study of TAF in HIV-infected patients without TAF dose modification.

1.3. Emtricitabine (FTC, Emtriva®)

Further information regarding Emtriva is available in the prescribing information, an overview is provided below.

1.3.1. General Information

Emtricitabine (5-fluoro-1-[(2R, 5S)-2-(hydroxymethyl)-[1, 3]-oxathiolan-5-yl] cytosine, FTC) is a NRTI that has demonstrated potent and selective inhibition of the HIV. In HIV-infected adults, FTC is administered as a 200 mg once daily dose concurrently with other ARV drugs. The 200 mg FTC capsule formulation was approved by the US FDA for marketing on 2 July 2003 and is available under the name Emtriva. In the European Union (EU), marketing authorization was granted for both the 200 mg Emtriva capsule formulation and a 10 mg/mL Emtriva oral solution formulation on 24 October 2003, with indications for the treatment of HIV infection concurrently with other ARV drugs in both adult and pediatric patients. In pediatric patients, the recommended dose of Emtriva is 6 mg/kg once daily, up to a maximum of 200 mg once daily when administered using the capsule formulation (for children weighing > 33 kg) or up to a maximum of 240 mg when administered using the oral solution formulation.

1.4. Fixed-Dose Combination of Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF)

Further information is available in the Prescribing Information for Truvada (emtricitabine/tenofovir disoproxil fumarate).

1.5. Rationale for This Study

Based on available data, the use of F/TAF for PrEP would provide a new option for persons with high sexual risk of HIV-1 acquisition. Based on data with F/TAF-based regimens used for treatment of chronic HIV-1 infection, the improved safety profile of F/TAF (relative to F/TDF) reduces the risk of a negative impact on bone mineralization in younger adults (18-25 years of age) who are still in a bone growth phase, and also reduces the risk of a negative impact on renal function in older adults with risk factors for chronic kidney disease. Use of F/TAF once daily for PrEP is expected to be similarly efficacious to Truvada but also have an improved safety profile.

Nonclinical pharmacology studies in rhesus macaques show that orally administered F/TAF, at doses resulting in PBMC exposures that are consistent with those achieved in humans administered a dose of F/TAF 200/25 mg, effectively prevents SHIV infection.

Oral administration of TAF results in rapid accumulation of TFV-DP in the intracellular PBMC compartment with levels that are at least 4-fold higher than with use of TDF. When used as monotherapy for 10 days (Study GS-US-120-0104), TAF 25 mg has increased antiviral potency relative to TDF 300 mg. Treatment of chronic HIV-1 infection with TAF-based regimens have similar or higher rates of undetectable viral load at 48 and 96 weeks when administered as Genvoya compared to STB in treatment-naive patients, and when administered as F/TAF + a third agent in virologically suppressed patients who switch from a Truvadabased regimen to F/TAF (Study GS-US-311-1089). Refer to the Genvoya Prescribing Information for more details.

There is considerable data demonstrating that F/TAF (administered as either Genvoya or as F/TAF + a third agent) has statistically significant improvement in both renal and bone safety profiles in both treatment-naive patients and in virologically suppressed patients who switch from a TDF based regimen (Refer to the Genvoya Prescribing Information for more details). These improvements in measures of renal and bone safety, most notably no reported cases of PRT (including Fanconi Syndrome), are most likely due to the 90% reduction in plasma TFV levels observed in participants receiving TAF-based regimens. The use of F/TAF for PrEP to reduce the risk of sexually acquired HIV-1 in uninfected individuals at high risk may provide an effective prevention regimen with a significantly improved renal and bone safety profile relative to Truvada. This is of particular importance for HIV-1–negative persons who are otherwise likely to be healthy, in whom the acceptability of medication related risks relative to benefit must be weighed carefully.

The present study will be conducted in MSM and transgender women (TGW) who are at least 18 years of age, a population consistently at highest risk of HIV-1 acquisition through sexual behavior.

1.6. Rationale for Dose

The 200 mg dose represents the dose of FTC in the FDC, Truvada, which is approved for a PrEP indication in the US.

Based upon results of the Phase 1 Study GS-US-120-0104, in which increasing doses of TAF (8 mg, 25 mg, and 40 mg) were administered to HIV-1–infected participants in 10 days of monotherapy, the range of plasma and PBMC exposure achieved with TAF 25 mg was chosen as the reference exposure. In this study, TAF 25 mg resulted in near-maximal antiviral activity with significantly increased TFV-DP levels in PBMCs and significantly decreased plasma TFV exposure relative to TDF.

The recommended dose of TAF is based on ensuring that patients have a TAF systemic exposure that is within the range of the reference exposure achieved with TAF 25 mg, or with TAF 10 mg when administered as Genvoya, for which an extensive efficacy and safety database exists. The recommended TAF dose (10 or 25 mg) is based on whether or not the co-administered third agent requires a PK enhancer. As F/TAF for PrEP will be administered in the absence of a third ARV agent, the 25 mg dose of TAF (with FTC 200 mg) has been selected for evaluation in the proposed Phase 3 study.

1.7. Risk/Benefit Assessment for the Study

During a pandemic, additional potential risks to participants may include adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 8 for further details on the risks and risk mitigation strategy.

1.8. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To assess the rates of HIV-1 infection in MSM and 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 participants 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 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 MSM and TGW who have sex with men who are administered daily F/TAF or F/TDF, when all participants have 96 weeks of follow up after randomization
- To compare the general safety between the treatments

CCI

3. STUDY DESIGN

3.1. Endpoints

3.1.1. Primary Endpoint

The primary endpoint will be the incidence of HIV-1 infection per 100 person years (PY) when all participants have a minimum follow up of 48 weeks and at least 50% of the participants have 96 weeks of follow up after randomization. HIV-1 infection is defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab:

Serologic evidence of seroconversion (reactive screening HIV Antigen [Ag]/Antibody [Ab] or Antibody test, confirmed by reactive HIV-1/HIV-2 differentiation assay), excluding HIV vaccinated participants, or

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

Evidence of acute HIV-1 infection (reactive p24 Ag or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Ab results).

Please refer to Appendix 7 for more details.

3.1.2. Secondary Endpoints

The key (α-controlled) secondary endpoints in the blinded phase are (in the following order):

- The percent change from baseline in hip BMD at Week 48 in a subset of participants
- The percent change from baseline in spine BMD at Week 48 in a subset of participants
- Assessment of renal biomarkers at Week 48
  - percent change from baseline in urine beta-2-microglobulin to creatinine ratio
  - percent change from baseline in urine RBP to creatinine ratio
  - distribution of urine protein (UP) and UPCR categories
- The change from baseline in serum creatinine at Week 48

Other secondary endpoints include:

The incidence of HIV-1 infection (as per Appendix 7) per 100 PY when all participants have 96 weeks of follow up after randomization

- The percent change from baseline in hip and spine BMD at Week 96 in the blinded phase in a subset of participants
- Assessment of renal biomarkers at Week 96 in the blinded phase
  - percent change from baseline in urine beta-2-microglobulin to creatinine ratio
  - percent change from baseline in urine RBP to creatinine ratio
  - distribution of UP and UPCR categories
- The change from baseline in serum creatinine at Week 96 in the blinded phase
- The incidence of treatment-emergent adverse events (AEs) and laboratory toxicities

CCI [redacted]

3.2. Study Design

This protocol describes a randomized, double-blind comparison of the safety and efficacy of F/TAF versus F/TDF administered once daily for at least 96 weeks in HIV-1–negative adult MSM or TGW (male at birth) who have sex with men and are at risk of HIV-1 infection.

All participants must meet all eligibility criteria in order to receive treatment in the study. Once randomized to receive treatment in the study, all participants must return to the study center for required visits at Weeks 4, 12, and every 12 weeks thereafter.

All participants will remain blinded to study drug for at least 96 weeks. The primary endpoint data will be collected and analyzed when all participants have a minimum follow up of 48 weeks and 50% of the participants have 96 weeks of follow up after randomization.

Once all participants have at least 96 weeks of follow up after randomization and upon notification by Gilead, all participants will return to the study center for an end of blinded treatment phase visit (may coincide with their next scheduled visit).

Participants who are still on blinded study drug at the end of blinded treatment phase visit will be offered entry into the OL phase of the study. CCI [redacted]

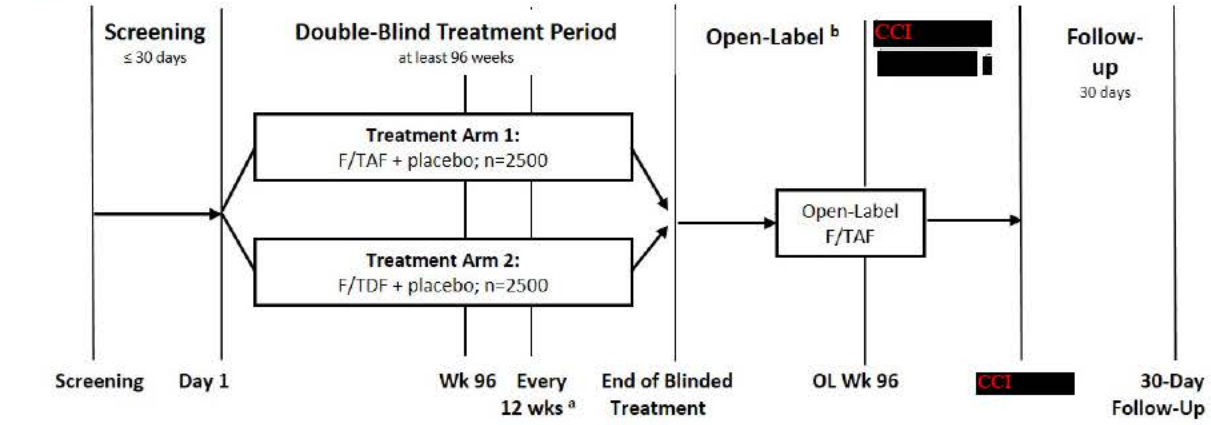
Participants who have discontinued study drug prior to the end of blinded treatment phase visit due to HIV infection will be eligible to continue participation in the OL phase up to OL Week 48, but will not be administered F/TAF once daily. From OL Week 48 participants who acquire HIV must complete the early study drug discontinuation (ESDD) visit and discontinue the study at the 30-Day Follow-up visit, 30 days after the last dose of study drug. Participants who have discontinued study drug for any other reason prior to the end of blinded treatment phase visit will not be eligible to participate in the OL phase.

CCI [redacted]

During the blinded treatment phase, participants may choose to continue to participate in the study without taking study drug ("on-study, off-study drug"). Participants 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 participant who has an ESDD visit and who will not continue participating in the study, or any participant 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.

DXA scans will be performed during regular intervals throughout the study (blinded and OL phase) in a subset of approximately 400 participants at a subset of sites (excluding Germany).

Figure 3-1. Study Schema



OL = open label; Wk = week

a Participants will continue blinded treatment until the last participant has reached Week 96, and upon notification by Gilead, all participants will return to the study center for the end of blinded treatment phase visits.

b Participants will continue in the OL phase every 12 weeks up to OL Wk 96.

[redacted]

3.3. Study Treatments

Blinded Phase:

Participants who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to one of the following 2 treatment arms:

- **Treatment Arm 1:** F/TAF (200 mg/25 mg) + placebo-to-match F/TDF (n = 2500)
- **Treatment Arm 2:** F/TDF (200 mg/300 mg) + placebo-to-match F/TAF (n = 2500)

Open Label Phase and Open Label Extension Phase:

During the OL phase and OL extension phase, all participants will be administered OL F/TAF (200 mg/25 mg).

[redacted]

CCI [redacted]

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Five thousand participants who meet all of the Inclusion and none of the Exclusion criteria will be enrolled.

4.2. Inclusion Criteria

Participants must be at high risk of sexual acquisition of HIV and meet *all* of the following inclusion criteria to be eligible for participation in this study.

1) HIV-1–negative status

2) MSM or TGW (male at birth) who have at least one of the following:

   a) condomless anal intercourse with at least 2 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

3) Age ≥ 18 years

4) Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min according to the Cockcroft-Gault formula for creatinine clearance {Cockcroft 1976}:

$$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = \text{CL}_{\text{cr}}(\text{mL/min})$$

5) Adequate liver and hematologic function:

- AST and alanine aminotransferase (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, and hemoglobin ≥ 10 g/dL

6) Willing and able to comply with study procedures

4.3. Exclusion Criteria

Participants who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Known hypersensitivity to the study drug, the metabolites, or formulation excipient.

2) Have a suspected or known active, serious infection(s)

3) Acute viral hepatitis A, B or C or evidence of chronic hepatitis B infection. Participants found to be susceptible to hepatitis B virus (HBV) infection should be referred for HBV vaccination. Participants found to be positive for hepatitis C virus (HCV) at screening must not have active infection or must have completed treatment and achieved a sustained virologic response.

4) Need for continued use of any contraindicated concomitant medications

5) Have an implanted defibrillator or pacemaker

6) Have a history of osteoporosis or bone fragility fractures

7) Current alcohol or substance abuse judged by the investigator to be problematic such that it potentially interferes with participant study compliance

8) Grade 3 or Grade 4 proteinuria or glycosuria that is unexplained or not clinically manageable.

9) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements

10) Have received investigational agents for the treatment or prevention of HIV-1 infection in the 30 days prior to screening

11) Participation in any other clinical trial (including observational trials) without prior approval from the sponsor is prohibited while participating in this trial

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

This is a randomized, double-blind study.

It is the responsibility of the investigator to ensure that the participant is eligible for the study prior to randomization.

Randomization cannot occur until participant eligibility has been confirmed. Once eligibility has been confirmed, each participant will be assigned a unique participant number using interactive voice/web response system (IXRS): either Interactive Web Response System (IWRS) or Interactive Mobile Response System (IMRS). Once a participant number has been assigned to a participant, it will not be reassigned to any other participant.

Participants will be randomized in a 1:1 ratio to Treatment Arm 1 or Treatment Arm 2.

IXRS will assign study drug bottle numbers at each study visit until the participant's last study visit. Study drug will be dispensed to the participant in a blinded fashion from Day 1 through the end of blinded treatment phase visit. All Day 1 visit tests and procedures must be completed prior to the administration of the first dose of the study drug. Initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit. Study drug will be dispensed to the participant in an OL fashion from the end of blinded treatment phase visit through the final study visit.

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain treatment assignment directly from the IXRS system for that participant. Gilead strongly recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine participant emergency medical care. The rationale for unblinding must be clearly explained in source documentation, along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study drug is critical for the integrity of this clinical study and therefore, if a participant's treatment assignment is disclosed to the investigator, the participant will have study drug discontinued. All participants will be followed until study completion unless consent to do so is specifically withdrawn by the participant.

Gilead Global Patient Safety (GLPS) (formerly Pharmacovigilance and Epidemiology) may independently unblind cases for expedited reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs).

5.2. Description and Handling

5.2.1. Formulation

5.2.1.1. Emtricitabine/Tenofovir Alafenamide (F/TAF) 200 mg/25 mg and Matching Placebo

Emtricitabine 200 mg/tenofovir alafenamide 25 mg tablets are blue, rectangular-shaped, filmcoated tablets, debossed with "GSI" on one side of the tablet and with "225" on the other side of the tablet. Each tablet core contains 200 mg of emtricitabine and 25 mg of tenofovir alafenamide. In addition to the active ingredients, the F/TAF tablets contain croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet cores are film-coated with FD&C blue #2/indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Placebo-to-match F/TAF tablets are identical in appearance to the active tablets and are blue, rectangular-shaped, film-coated tablets. Placebo tablets contain croscarmellose sodium, magnesium stearate, lactose and microcrystalline cellulose. The tablet cores are film-coated with Blue #2/indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

5.2.1.2. Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) Tablets and Matching Placebo

Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg tablets are blue, capsule-shaped, film-coated tablets debossed with "GILEAD" on one side and are plain-faced on the other side of the tablet. Each tablet core contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. In addition to active ingredients, the F/TDF tablets contain microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, lactose monohydrate and magnesium stearate. The tablet cores are film coated with FD&C blue #2/indigo carmine aluminum lake, lactose monohydrate, hypromellose, titanium dioxide and triacetin.

Placebo-to-match F/TDF tablets are identical in appearance to the active tablets and are blue, capsule-shaped, film-coated tablets. Placebo tablets contain denatonium benzoate, lactose monohydrate, pregelatinized starch, croscarmellose sodium and magnesium stearate. The tablet cores are film-coated to mask taste. The film coating consists of FD&C blue #2/indigo carmine aluminum lake, lactose monohydrate, hypromellose, titanium dioxide, and triacetin.

5.2.2. Packaging and Labeling

Emtricitabine/Tenofovir Alafenamide (F/TAF) tablets and placebo-to-match F/TAF tablets are packaged in a white high-density polyethylene (HDPE) bottle. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed and aluminum-faced liner.

Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) tablets and placebo-to-match F/TDF tablets are packaged in a white HDPE bottle. Each bottle contains 30 tablets and silica gel desiccant. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed and aluminum-faced liner.

Study drug(s) bottles to be distributed to centers in the US and EU shall be labeled to meet all applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations as applicable.

5.2.3. Storage and Handling

Emtricitabine/Tenofovir Alafenamide (F/TAF) and the placebo-to-match F/TAF tablets should be stored at a controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label.

Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) and the placebo-to-match F/TDF tablets should be stored at a controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label.

Until dispensed to the participants, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration

Emtricitabine/Tenofovir Alafenamide (F/TAF), placebo-to-match F/TAF, F/TDF, and placebo-to-match F/TDF tablets will be provided by Gilead. Study drug will be dispensed to participants at the Day 1 visit. Participants will be instructed to take their first dose of study medication following completion of the study procedures at the Day 1 visit. Initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit and after the investigator has confirmed eligibility with the participant.

Participants will be instructed to bring all study medication in the original container at each clinic visit for drug accountability.

5.4. Prior and Concomitant Medications

Medications and use of herbal/natural supplements listed in the following table are excluded or should be used with caution while participants are taking study drug on the study due to potential drug-drug interactions with F/TAF.

Table 5-1. Prior and Concomitant Medications

Medication Class	Medications to be Used with Caution	Prohibited Medications
Antiarrhythmics	amiodarone, quinidine: May increase concentration of TAF and/or TFV	
Anticonvulsants		carbamazepine, oxcarbazepine, phenobarbital, phenytoin
Antimycobacterials	clarithromycin: may increase concentration of TAF and/or TFV	rifapentine, rifabutin, rifampin
Antifungals	itraconazole, ketoconazole, voriconazole: may increase concentration of TAF and/or TFV	
Calcium channel blockers	diltiazem, felodipine, verapamil: may increase concentration of TAF and/or TFV	
Digoxin	Concomitant use may result in an increased or decreased digoxin concentration; use with caution and with appropriate monitoring of serum digoxin concentrations.	
Herbal/Natural Supplements		St. John's Wort, echinacea, milk thistle (eg, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Hepatitis C therapies	Ledipasvir/sofosbuvir: has been shown to increase tenofovir exposure	boceprevir, telaprevir
Nephrotoxic medications	high dose or multiple NSAIDS	systemic chemotherapeutic agents, aminoglycoside antibiotics, amphotericin B, cidofovir, cisplatin, foscarnet, IV pentamidine, or, other agents with significant nephrotoxic potential
Systemic glucocorticoids		dexamethasone (more than 1 dose), or chronic use of other systemic glucocorticoids
Other		Probenecid

NSAIDS = nonsteroidal anti-inflammatory drugs

Should participants have a need to initiate treatment with any prohibited concomitant medication, the Gilead medical monitor must be consulted and approval granted prior to initiation of the new medication. In instances where a prohibited medication is initiated prior to discussion with the sponsor, the investigator must notify Gilead as soon as he/she is aware of the use of the prohibited medication.

There are no substantial safety data regarding the concomitant administration of the coronavirus disease 2019 (COVID-19) vaccines and F/TAF. Participants are allowed to receive the COVID-19 vaccine, and study visits should continue as planned if vaccination occurs while the participant is on the study. Investigators should follow local guidelines for concomitant administration of the COVID-19 vaccines with the study drugs.

5.5. Dispensing and Accountability of Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused Investigational Medicinal Product (IMP) or study drug. The investigator [or designee (eg, study center pharmacist)] will acknowledge receipt of the study drugs from Gilead (or designee) after reviewing the shipment's content and condition. The investigator (or designee) will be responsible for maintaining an accurate inventory (on study drug accountability records) of the dates and quantities of all study drugs received, dispensed, and returned. The requirements of all applicable Federal and State drug dispensing laws will apply to all doses of study drugs dispensed by the investigator (or designee).

The study drug inventory and dispensing logs must be available for inspection by the study monitor. Study drug supplies, including partially used or empty bottles, must be accounted for by the study monitor prior to destruction or return.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant enrolled in the study are presented in tabular form in Appendix 2 and Appendix 3 and described in the text that follows. The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Participant Enrollment and Treatment Assignment

It is the responsibility of the investigator to ensure that participants are eligible for study prior to enrollment.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

The following assessments will be performed at the screening visit:

- Written informed consent completed prior to any other assessments
- Medical history including information about alcohol use in the past year and self-reported sexual risk events and medications used by the participant in the 30 days prior to the screening visit
- Complete physical examination, vital signs measurements (blood pressure, pulse, respiration rate, and temperature), height, and weight
- Sexually transmitted infection (STI) testing. Participants who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the participant at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- Fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test. If test is positive, a retest will be completed. If the retest is positive, the participant is a screen failure.
  - Any participant with a positive repeat HIV-1 rapid test will receive counseling and be referred for appropriate care

- Urine sample for dipstick urinalysis (per local lab)
- Urine sample for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine)
  - Participants who test positive for Grade 3 or Grade 4 proteinuria or glycosuria that is unexplained or not clinically manageable will be excluded from the study
- Blood sample collection for the following central laboratory analyses:
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Chemistry profile: alkaline phosphatase, AST, ALT, gamma glutamyltransferase (GGT), total bilirubin, direct and indirect bilirubin, total protein, albumin, lactate dehydrogenase (LDH), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in participants with total amylase > 1.5 × ULN)
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - Lipid panels (total cholesterol, high-density lipoprotein [HDL], direct low-density lipoprotein [LDL], and triglycerides). It is recommended that participants fast for 8 hours prior to the blood draw.
  - HIV testing
    - HIV-1 Ab/Ag
    - HIV-1 RNA by polymerase chain reaction (PCR) for those participants who show symptoms consistent with acute infection and who have a negative fourth generation rapid HIV-1 Ab/Ag test or third generation rapid HIV-1 Ab test
    - Any participant with HIV-1 Ab/Ag or an HIV-1 infection (per Appendix 7) is a screen failure and will receive counseling and be referred for appropriate care
  - Hepatitis B testing (hepatitis B virus surface antigen [HBsAg], hepatitis B virus surface antibody [HBsAb], hepatitis B virus core antibody [HBcAb])
    - If a participant has a negative HBsAg, negative HBsAb, and positive HBcAb, HBV DNA testing will be completed. If the HBV DNA result is positive, the participant is a screen failure.
    - Participants found to be susceptible to HBV infection should be referred for HBV vaccination

— Hepatitis C testing

■ If the HCV Ab result is positive, then HCV RNA will be completed unless there is documented evidence that sustained virologic response has been achieved. If the HCV RNA result is positive, the participant is a screen failure

- Computer-assisted self-interview (CASI) for: recent sexual risk events; interest in using PrEP; self-identification of transgender status; education and employment history; and use of tobacco and recreational drugs

- Risk reduction counseling including provision of condoms

6.2.2. Day 1 Visit (Baseline)

Day 1 procedures and randomization may occur as soon as all eligibility criteria are confirmed. The Day 1 visit must occur within 30 days after the screening visit. The participant must complete all Day 1 procedures before being dispensed study drug. Initiation of treatment with study drug must take place within 24 hours after the Day 1 visit.

- Fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test. If test is positive, a retest will be completed. If the retest is positive, the participant will no longer be permitted to participate in the study.

  — A negative HIV-1 RNA by PCR result is required prior to receiving study drug for those participants who show symptoms consistent with acute infection and who have a negative HIV-1 rapid test

  — Any participant with a positive repeat HIV-1 rapid test or HIV-1 infection (per Appendix 7) will receive counseling and be referred for appropriate care

- Review of AEs and changes in concomitant medications, including assessment of whether STIs were diagnosed and any treatments were received since the screening visit

- Targeted (symptom directed) physical examination and vital signs (blood pressure, pulse, respiration rate, and temperature) if the Day 1 visit is > 7 days after the screening visit

- Weight

- CASI for sexual risk events since the last visit

- Randomization in IXRS if all screening assessments meet eligibility criteria

- Drug dispensation

- Adherence and risk reduction counseling including provision of condoms. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site immediately for evaluation and HIV-1 testing if they develop such symptoms. Investigator or site support staff must emphasize the importance of the use of barrier protection during the first 2 weeks from baseline.
- CCI [redacted]
- Record any serious adverse events (SAEs) and all AEs related to protocol-mandated procedures occurring after signing of the informed consent form (ICF).

Throughout the study, participants may be asked to provide daily information on adherence and sexual risk events through the use of a diary. Participants may also receive periodic contacts to remind them to take their study drug and to provide any additional support needed.

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-mandated procedures on the adverse events electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Treatment Assessments Blinded Phase (Weeks 4, 12, and Every 12 Weeks Until the end of blinded treatment phase visit)

The following evaluations are to be completed at the Weeks 4, 12, and every 12 weeks visits until the end of blinded treatment phase visit unless otherwise specified.

All study visits are to be scheduled relative to the Day 1 visit date. Study visits are to be completed within ± 2 days of the protocol-specified visit date based on the Day 1 visit through Week 12 and study visits thereafter completed within ± 14days of the protocol-specified visit date through the end of blinded treatment phase visit, unless otherwise specified.

Regularly scheduled evaluations will be performed for all participants whether or not they continue to receive study drug, unless otherwise specified.

- Targeted (symptom directed) physical examination (complete physical examination at Weeks 48 and 96 only)
- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit
- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)

- Weight
- STI testing. Participants who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the participant at the discretion of the investigator (rectal swab not required at Week 4).
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- Fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test (**not done for HIV-infected participants**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
- Urine collection for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine), and sample storage
- Blood sample collection for the following central laboratory analyses:
  - Hematology profile: CBC with differential and platelet count
  - 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 participants with total amylase > 1.5 × ULN)
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - Lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). Participants should be instructed to fast (no food or drinks, except water, at least 8 hours prior to blood collection) (**every 24 weeks**)
  - HIV-1 Ab/Ag ~~(~~not done for participants who acquire HIV~~)~~
    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.

— HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 6) and sample collection for possible genotypic resistance testing for any participants who:

1) have a positive retest rapid HIV-1 Ab/Ag test (either fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab 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

5) have been confirmed HIV-infected

For details regarding confirmation of HIV infection, please refer to Section 6.11.

— Hepatitis B testing (HBsAg, HBsAb, HBcAb) (**every 24 weeks**)

- If a participant has a negative HBsAg, negative HBsAb, and positive HBcAb, HBV DNA testing will be completed.
    - Participants who have tested positive for HBcAb on the study during a prior visit do not need to repeat the Hepatitis B testing panel during subsequent visits and instead will have HBV DNA testing performed at visits every 24 weeks
- If the HBsAg or HBV DNA result is positive, the participant will be discontinued and referred to appropriate HBV treatment. If the participant has acquired HIV, they may continue participation in the study at the discretion of the investigator.

— Hepatitis C testing (**every 48 weeks**)

- If the HCV Ab result is positive, then HCV RNA will be completed unless there is documented evidence that sustained virologic response has been achieved. If the HCV RNA result is positive, the participant may continue in the study at the discretion of the investigator.
- Participants who have tested positive for HCV Ab on the study during a prior visit do not need to repeat the HCV Ab test during subsequent visits and instead will have HCV RNA testing performed at visits every 48 weeks

CCI [redacted]

CCI [redacted]

CCI [redacted]

— Plasma sample storage for virology, safety, and/or PK testing

— CD4, CD8, and CD4/CD8 ratio (**only for participants who acquire HIV**)

— Large volume blood draw for the following (only for participants who acquire HIV. All blood draws will be done at the first study visit upon confirmation of HIV infection, and at the additional timepoints as indicated below. Subsequent draws will be performed at the participants' regularly scheduled study visit):

  ■ Latent and Active Reservoir assessment (24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter)

  ■ T cell response and phenotype (24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter)

  ■ Viral Sequence Diversity assessment (**24 weeks after HIV infection only**)

— Inflammatory/immune activation biomarkers (only for participants who acquire HIV. Done at the first study visit upon confirmation of HIV infection, at 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter)

- CASI for sexual risk events and adherence since the last visit
- Collect and review used and unused blinded study drug for accountability and calculate compliance (**not done for participants who have permanently discontinued study drug**)
- Drug dispensation (not done for participants who have been or will be permanently discontinued from study drug)
- Adherence and risk reduction counseling including provision of condoms. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing if they develop such symptoms. (**Adherence and risk reduction counseling not done for participants who acquire HIV.**)
- Participants may be asked to provide daily information on adherence and sexual risk events through the use of a diary

CCI [redacted]

6.4. End of Blinded Treatment Phase Visit

Once all participants have had at least 96 weeks of follow up after randomization and upon notification by Gilead, all participants will return to the study center for an end of blinded treatment phase visit (may coincide with their next scheduled study visit).

CCI [redacted]

Participants who do not participate in the OL phase will discontinue their blinded study drug and will return for a 30-Day Follow-Up visit following the end of blinded treatment phase visit.

The following will be performed at the end of blinded treatment phase visit:

- Targeted (symptom directed) physical examination
- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since the last visit
- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Weight
- STI testing. Participants who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the participant at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- Fourth generation rapid HIV-1 Ag/Ab or third generation rapid HIV-1 Ab test (**not done for participants who acquire HIV**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.

- Urine collection for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine), and sample storage

- Blood sample collection for the following central laboratory analyses:

  — Hematology profile: CBC with differential and platelet count

  — 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 participants with total amylase > 1.5 × ULN)

  — Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance

  — HIV-1 Ab/Ag (not done for participants who acquire HIV)

    ■ If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.

  — HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 6) and sample collection for possible genotypic resistance testing for any participants who:

    1) have a positive retest rapid HIV-1 Ab/Ag test (either fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab 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

    5) have been confirmed HIV-infected

  For details regarding confirmation of HIV infection, please refer to Section 6.11.

  — Hepatitis B testing (HBsAg, HBsAb, HBcAb) (**if > 24 weeks from prior testing**)

    ■ If a participant has a negative HBsAg, negative HBsAb, and positive HBcAb, HBV DNA testing will be completed.

      ○ Participants who have tested positive for HBcAb on the study during a prior visit do not need to repeat the Hepatitis B testing panel during subsequent visits and instead will have HBV DNA testing performed at visits every 24 weeks

- If the HBsAg or HBV DNA result is positive, the participant will be discontinued and referred to appropriate HBV treatment. If the participant has acquired HIV, they may continue in the study at the discretion of the investigator.

— Hepatitis C testing (if > 48 weeks from prior testing)

- If the HCV Ab result is positive, then HCV RNA will be completed. If the HCV RNA result is positive, the participant may continue in the study at the discretion of the investigator.
- Participants who have tested positive for HCV Ab on the study during a prior visit do not need to repeat the HCV Ab test during subsequent visits and instead will have HCV RNA testing performed at visits every 48 weeks

CCI [redacted]

CCI [redacted]

— Plasma sample storage for virology, safety, and/or PK testing

— CD4, CD8, and CD4/CD8 ratio (**only for participants who acquire HIV**)

— Large volume blood draw for the following (only for participants who acquire HIV. All blood draws will be done at the first study visit upon confirmation of HIV infection and at the additional time points as indicated below. Subsequent draws will be performed at the participants' regularly scheduled study visit):

- Latent and Active Reservoir assessment (24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter)
- T cell response and phenotype (24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter)
- Viral Sequence Diversity assessment (**24 weeks after HIV infection only**)

— Inflammatory/immune activation biomarkers (only for participants who acquire HIV. Done at the first study visit upon confirmation of HIV infection, at 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter)

- CASI for sexual risk events and adherence since the last visit
- Collect and review used and unused blinded study drug for accountability and calculate compliance (**not done for participants who have permanently discontinued study drug**)

- OL drug dispensation (**not done for participants who acquire HIV**). If the participant has already taken a dose of blinded study drug on the day of the end of blinded treatment phase visit, they should not begin dosing with OL F/TAF until the next day. If the participant has not taken a dose of blinded study drug on the day of the visit, they should take their first dose of OL F/TAF on the same day of the end of blinded treatment phase visit.

- Adherence and risk reduction counseling including provision of condoms. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing if they develop such symptoms. (**Adherence and risk reduction counseling not done for participants who acquire HIV.**)

[redacted]

6.5. Treatment Assessments Open-Label Phase and Open-Label Extension Phase

All study visits in the OL phase and OL extension phase are to be scheduled relative to the end of blinded treatment phase visit date. Study visits are to be completed within ± 14 days of the protocol-specified visit date based on the end of blinded treatment phase visit. Participants participating in the OL phase and OL extension phase will return for study visits every 12 weeks.

From OL Week 48, participants who acquire HIV must complete the ESDD visit and discontinue the study at the 30-Day Follow-up visit, 30 days after the last dose of study drug.

[redacted]

6.5.1. Open-Label Phase (Prior to OL Week 96)

Regularly scheduled evaluations will be made on all participants, unless otherwise specified.

- Targeted (symptom directed) physical examination (**complete physical examination at OL Week 48 only**)

- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit

- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)

- Weight

- STI testing. Participants who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the participant at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- Fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test (**not done for participants who acquire HIV**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
- Urine collection for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine), and sample storage
- Blood sample collection for the following central laboratory analyses:
  - Hematology profile: CBC with differential and platelet count
  - 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 participants with total amylase > 1.5 × ULN)
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - Lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) Participants should be instructed to fast (no food or drinks, except water, at least 8 hours prior to blood collection) (**every 24 weeks**)
- HIV-1 Ab/Ag (not done for participants who acquire HIV)
    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.
  - HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 6) and sample collection for possible genotypic resistance testing for any participants who:

1) have a positive retest rapid HIV-1 Ab/Ag test (either fourth generation rapid HIV1 Ab/Ag or third generation rapid HIV-1 Ab 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

5) have been confirmed HIV-infected

For details regarding confirmation of HIV infection, please refer to Section 6.11.

— Hepatitis B testing (HBsAg, HBsAb, HBcAb) (**every 24 weeks**)

- If a participant has a negative HBsAg, negative HBsAb, and positive HBcAb, HBV DNA testing will be completed.
  - Participants who have tested positive for HBcAb on the study during a prior visit do not need to repeat the Hepatitis B testing panel during subsequent visits and instead will have HBV DNA testing performed at visits every 24 weeks
- If the HBsAg or HBV DNA result is positive, the participant will be discontinued and referred to appropriate HBV treatment. If the participant has acquired HIV, they must complete the ESDD visit and discontinue the study at the 30-Day Follow-up visit, 30 days after the last dose of study drug.

— Hepatitis C testing (**every 48 weeks**)

- If the HCV Ab result is positive, then HCV RNA will be completed. If the HCV RNA result is positive, the participant may continue in the study at the discretion of the investigator.
- Participants who have tested positive for HCV Ab on the study during a prior visit do not need to repeat the HCV Ab test during subsequent visits and instead will have HCV RNA testing performed at visits every 48 weeks

CCI [redacted]

CCI [redacted]

— Plasma sample storage for virology, safety, and/or PK testing

— CD4, CD8, and CD4/CD8 ratio (**only for participants who acquire HIV**)

— Large volume blood draw for the following (only for participants who acquire HIV [up to OL Week 48]. All blood draws will be done at the first study visit upon confirmation of HIV infection, and at the additional time points as indicated below. Subsequent draws will be performed at the participants' regularly scheduled study visit):

  - Latent and Active Reservoir assessment (24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter up to OL Week 48)
  - T cell response and phenotype (24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter up to OL Week 48)
  - Viral Sequence Diversity assessment (**24 weeks after HIV infection only, up to OL Week 48**)

— Inflammatory/immune activation biomarkers (only for participants who acquire HIV. Done at the first study visit upon confirmation of HIV infection, at 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter up to OL Week 48)

- CASI for sexual risk events and adherence since the last visit
- Collect and review used and unused study drug for accountability and calculate compliance (**not done for participants who acquire HIV**)
- Drug dispensation (not done for participants who acquire HIV)
- Adherence and risk reduction counseling including provision of condoms. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing if they develop such symptoms. (**Adherence and risk reduction counseling not done for participants who acquire HIV.**)
- Participants may be asked to provide daily information on adherence and sexual risk events through the use of a diary

[redacted]

6.5.2. Open-Label Extension Phase (From OL Week 96)

The following assessments are to be completed at every visit for participants continuing in the OL extension phase, unless otherwise specified. For participants who choose not to continue in the OL extension phase, the ESDD assessments (prior to OL Week 96) should be completed.

- Targeted (symptom directed) physical examination (**every 24 weeks**)

- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature) (every 24 weeks)
- Weight (every 24 weeks)
- STI testing. Participants who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the participant at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- At a minimum, fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
- Blood sample collection for the following central laboratory analyses:
  - Chemistry profile: bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, sodium (**every 24 weeks**)
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance (**every 24 weeks**)
  - CCI [redacted]
  - HIV-1 Ab/Ag
    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.
  - HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 6) and sample collection for possible genotypic resistance testing for any participants who:

1) have a positive retest rapid HIV-1 Ab/Ag test (either fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab 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

5) have been confirmed HIV-infected

For details regarding confirmation of HIV infection, please refer to Section 6.11.

— Hepatitis B testing (HBsAg, HBsAb, HBcAb) (**every 48 weeks**)

- If a participant has a negative HBsAg, negative HBsAb, and positive HBcAb, HBV DNA testing will be completed.
  - Participants who have tested positive for HBcAb on the study during a prior visit do not need to repeat the Hepatitis B testing panel during subsequent visits and instead will have HBV DNA testing performed at visits every 48 weeks.
- If the HBsAg or HBV DNA result is positive, the participant will be discontinued and referred to appropriate HBV treatment. If the participant has acquired HIV, they will discontinue the study, receive counseling, and be referred for appropriate care.

— Hepatitis C testing (**every 48 weeks**)

- If the HCV Ab result is positive, then HCV RNA will be completed. If the HCV RNA result is positive, the participant may continue in the study at the discretion of the investigator.
- Participants who have tested positive for HCV Ab on the study during a prior visit do not need to repeat the HCV Ab test during subsequent visits and instead will have HCV RNA testing performed at visits every 48 weeks.

CCI [redacted]

- Collect and review used and unused study drug for accountability and calculate compliance
- Drug dispensation
- Adherence and risk reduction counseling including provision of condoms. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing if they develop such symptoms.

6.6. Unscheduled Visits

Additional unscheduled assessments may be performed at the discretion of the investigator (eg, for evaluation of AEs and/or laboratory abnormalities, including assessment of whether any STIs were diagnosed and any treatments were received since last visit). Participants who test HIV positive during an unscheduled visit will have a DBS sample collected.

6.7. Posttreatment Assessments

6.7.1. Early Study Drug Discontinuation Assessments (Prior to OL Week 96)

If the participant discontinues study drug prior to the OL Week 96 visit, the participant will be asked to return to the clinic within 72 hours of stopping study drug for the ESDD visit.

- Targeted (symptom directed) physical examination
- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit
- When clinically indicated, vital signs measurements (blood pressure, pulse, respiration rate, and temperature)
- Weight
- STI testing. Participants who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the participant at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- Fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test (**not done for participants who acquire HIV**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
- Urine collection for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine), and sample storage

- Blood sample collection for the following central laboratory analyses:

  — Hematology profile: CBC with differential and platelet count

  — 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 participants with total amylase > 1.5 × ULN)

  — Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance

  — HIV-1 Ab/Ag (not done for participants who acquire HIV)

    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.

  — HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 6) and sample collection for possible genotypic resistance testing for any participants who:

    1) have a positive retest rapid HIV-1 Ab/Ag test (either fourth generation rapid HIV-1 Ab/Ag or third-generation rapid HIV-1 Ab 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

    5) have been confirmed HIV-infected

  For details regarding confirmation of HIV infection, please refer to Section 6.11.

  CCI [redacted]

  — Plasma sample storage for virology, safety, and/or PK testing

  — CD4, CD8, and CD4/CD8 ratio (**only for participants who acquire HIV**)

- CASI for sexual risk events and adherence since the last visit

- Collect and review used and unused study drug for accountability and calculate compliance

CCI [redacted]

6.7.2. Early Study Drug Discontinuation Assessments (From OL Week 96)

If the participant discontinues study drug from OL Week 96 visit, the participant will be asked to return to the clinic within 72 hours of stopping study drug for the ESDD visit.

- Targeted (symptom directed) physical examination
- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit
- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Weight
- STI testing. Participants who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the participant at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- At a minimum fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test (**not done for participants who acquire HIV**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
- Blood sample collection for the following central laboratory analyses:
  - Chemistry profile: bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, sodium
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - HIV-1 Ab/Ag (not done for participants who acquire HIV)
    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.

— HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 6) and sample collection for possible genotypic resistance testing for any participants who:

1) have a positive retest rapid HIV-1 Ab/Ag test (either fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab 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

5) have been confirmed HIV-infected

For details regarding confirmation of HIV infection, please refer to Section 6.11.

— CD4, CD8, and CD4/CD8 ratio (for participants that acquire **HIV**)

- Collect and review used and unused study drug for accountability and calculate compliance

  At the ESDD visit, any evaluations showing abnormal results that the investigator determines to have a possible or probable causal relationship with the study drug, will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

6.7.3. 30-Day Follow-Up Assessment

All participants who have received at least one dose of study drug will be required to complete a follow-up visit 30 days (+ 14 days) after discontinuation of the study drug. Participants 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.

At the 30-Day Follow-Up visit, **any evaluations showing abnormal results that the investigator determines to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained**.

The following evaluations are to be completed at the 30-Day Follow-Up visit (**Prior to OL Week 96)**:

- Targeted (symptom directed) physical examination

- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit

- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Weight
- STI testing. Participants who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the participant at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- Fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test (**not done for participants who acquire HIV**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
- Urine collection for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine), and sample storage
- Blood sample collection for the following central laboratory analyses:
  - Hematology profile: CBC with differential and platelet count
  - 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 participants with total amylase > 1.5 × ULN)
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - HIV-1 Ab/Ag (not done for participants who acquire HIV)
    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.
  - HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 6) and sample collection for possible genotypic resistance testing for any participants who:

1) have a positive retest rapid HIV-1 Ab/Ag test (either fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab 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

5) have been confirmed HIV-infected

For details regarding confirmation of HIV infection, please refer to Section 6.11.

— Plasma sample storage for virology, safety, and/or PK testing

— CD4, CD8, and CD4/CD8 ratio (**only for participants who acquire HIV**~~)~~

The following evaluations are to be completed at the 30-Day Follow-Up visit (**From OL Week 96)**:

- Targeted (symptom directed) physical examination
- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit
- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Weight
- STI testing. Participants who test positive for any STI will be treated in accordance with local STI guidelines.

  — Genital, rectal, and pharyngeal examination as appropriate

  — Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the participant at the discretion of the investigator.

  — Urine sample for gonorrhea and chlamydia (per central lab)

  — Blood sample for syphilis testing (per local lab)

- At a minimum, fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test (**not done for participants who acquire HIV**)

- If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.

- Blood sample collection for the following central laboratory analyses:

  - Chemistry profile: bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, sodium

  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance

  - HIV-1 Ab/Ag (not done for participants who acquire HIV)

    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.

  - HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 6) and sample collection for possible genotypic resistance testing for any participants who:

    1) have a positive retest rapid HIV-1 Ab/Ag test (either fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab 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

    5) have been confirmed HIV-infected

    For details regarding confirmation of HIV infection, please refer to Section 6.11.

  - CD4, CD8, and CD4/CD8 ratio (only for participants who acquire **HIV)**

6.8. Criteria for Restarting Study Drug After an Interruption

If a participant interrupts study dosing temporarily for more than 14 consecutive days, the participant should have samples collected for the following HIV tests prior to restarting study dosing:

- At a minimum, fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test

— If the result for rapid HIV testing is positive, a retest will be completed. If the retest is positive, the participant must not restart study drug, and may opt to begin a full HIV treatment regimen until the HIV-1 diagnosis is confirmed, at investigator discretion {Center for Disease Control and Prevention (CDC) 2018}.

— Upon testing negative for the rapid HIV-1 test, the participant may restart study dosing while pending the central lab HIV tests, at the investigator's discretion.

- HIV-1 Ab/Ag (per central lab)
- HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing (per central lab)

For details regarding confirmation of HIV infection, please refer to Section 6.11.

6.9. Criteria for Discontinuation of Study Treatment

If a participant discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow up and procedures until the end of blinded treatment phase visit. If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

Study medication will be discontinued as applicable in the following instances:

- HIV-1 infection is confirmed
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the participant's best interest
- Participant request to discontinue for any reason

Study medication may be discontinued as applicable in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the participant may resume study dosing at the discretion of the investigator (see Section 6.8 for criteria for restarting study drug after an interruption).
- Participant noncompliance
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board (IRB) or independent ethics committee (IEC)

6.10. Bone Evaluations

In a subset of participants (except in Germany), DXA scans of the hip and spine will be performed throughout the study.

During the blinded phase of the study, all DXA substudy participants will have scans at Day 1, Week 48, Week 96, and end of blinded treatment phase visits. CCI [redacted].

The Day 1 scan must be completed ± 14 days from start of treatment. All other scans should be completed ± 6 weeks of the protocol-specified visit date.

DXA substudy participants who plan to temporarily interrupt study drug for more than 14 days should have the DXA scans performed within 14 days of the last dose of study drug, unless the participant has had scans performed for a Week 48, Week 96, end of blinded treatment Phase. CCI [redacted].

DXA scans will be completed at the ESDD visit if the ESDD visit is > 12 weeks after the previous DXA scan. Participants who have permanently discontinued study drug will not have DXA scans performed during subsequent study visits.

DXA scans will cover the spine and hip to measure changes in BMD. DXA scan results will be provided to study sites as they become available.

A complete description of the procedures performed for the DXA scans will be provided in a DXA manual.

6.11. HIV Infection

Participants will be assessed for any recent exposures that the investigator considers high risk for HIV infection at each study visit (including phone contacts and any unscheduled visits) from randomization through the end of study, with HIV testing done as clinically appropriate.

Participants with results confirming HIV infection (per Appendix 7) will immediately discontinue study drug, receive counseling, and be referred for appropriate care. If the participant's HIV-1 RNA is > 400 copies/mL, the stored sample for possible genotypic resistance will be sent for testing. An ESDD visit should also be completed within 72 hours of the participant's last dose of study drug.

Once HIV infection is confirmed (per Appendix 7), all records pertaining to the event including laboratory results, clinic notes, prescribed medications, and other relevant information (including local records and records from other clinics) should be collected and submitted together with the HIV-1 infection questionnaire.

After OL Week 48, participants who acquire HIV must complete ESDD visit and discontinue the study at the 30-Day Follow up visit, 30 days after the last dose of study drug.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. AEs may also include pre-treatment or posttreatment complications that occur as a result of protocol-specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures performed (eg, elective procedures, surgery, endoscopy, tooth extraction, transfusion). The condition that led to the procedure may be an adverse event and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.5.)

Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram [ECG], X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin). For specific information on handling of clinical laboratory abnormalities in this study, please refer to Appendix 4.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

Severity should be recorded and graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 5). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

7.3.1. Requirements for Collection Prior to Study Drug Initiation:

Prior treatment history is collected as part of the study entry criteria and evaluation of individual patient characteristics and will not be generating lack of effect reports as this is outside the scope of the present clinical study. However, investigators should report any cases of lack of effect that they feel appropriate regarding the previous treatment regimen as spontaneous reports to the relevant authorities or marketing authorization holders.

After informed consent, but prior to initiation of study drug, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug must be reported to the eCRF database as instructed.

All AEs should be followed until resolution or until the adverse event is stable. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the protocol-required posttreatment follow-up period, must be reported on the applicable eCRFs and Gilead GLPS as instructed below. This also includes any SAEs resulting from protocol-associated procedures performed after ICF is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 30 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to Gilead GLPS.

Instructions for reporting SAEs are described in Section 7.3.3.1.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the event description section of the SAE eCRF.

Follow up of AEs will continue through the last day on study (including the follow-up off-study drug period of the study) and/or until the investigator and/or Gilead determine that the participant's condition is stable. Gilead may request that certain AEs be followed until resolution.

7.3.3.1. Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel will record all SAE data in the eCRF database and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

- If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper serious adverse event report form and submit by e-mail or fax within 24 hours of the investigator's knowledge of the event to:

Gilead GLPS contact information:	Email:	PPD
	Fax:	PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the event description section of the Safety Report eCRF.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs which may be in the form of line-listings, serious adverse drug reactions (SADRs), or SUSARs. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB/IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Special Situations

Special situation reports include reports of medication error, abuse, misuse, or overdose, occupational exposure with an AE, and reports of adverse reactions associated with product complaints. Medication error is any preventable event that can cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare professional, patient or consumer. Abuse is defined as persistent, sporadic or intentional excessive use of a medicinal product by a patient accompanied by harmful, physical, and/or psychological effects. Misuse is defined as any use of a medicinal product in a way that is not in

accordance with the protocol instructions or the local prescribing information and may be accompanied by harmful physical and/or psychological effects. An overdose is defined as a dose taken (accidentally or intentionally) exceeding the dose as prescribed by the protocol or the maximal recommended daily dose as stated in the Product Labeling, specifically notated in the IB, (as it applies to the daily dose for the participant/patient in question). Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or nonprofessional occupation.

In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s) or the investigator has reason to suspect that the participant has taken the additional dose(s).

Product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging or distribution of the product.

7.5.1. Reporting Special Situations

Electronic Special Situations Reporting

- Site personnel record all special situations data in the eCRF database and from there transmit the special situations information to Gilead GLPS within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If it is not possible to record and submit the special situations information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the information on the paper special situations report form and submit by e-mail or fax within 24 hours of the investigator's knowledge of the event to:

Gilead GLPS contact information:	Email: Fax:	PPD PPD

- As soon as it is possible to do so, any special situations reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.
- If any special situations have been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- All special situations data will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Additional information may be requested to ensure the timely completion of accurate special situations reports. Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report eCRF; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be recorded on the AE eCRF.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 7.5 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.6. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 4 as outlined below.

- All clinically significant Grade 3 and 4 laboratory abnormalities should be repeated within 3 calendar days to confirm toxicity grade. Confirmation of toxicity grade is required prior to the next dose of study drug for any Grade 3 and 4 laboratory abnormality that in the opinion of the investigator is clinically significant and may pose a risk to the participant's safety.
- Clinical events and clinically significant laboratory abnormalities will be graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (refer to Appendix 5).

Any questions regarding toxicity management should be directed to the medical monitor.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.6.2. Grades 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ Grade 2.
- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with study drug and is considered related to study drug, then study drug should be permanently discontinued and the participant managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to study drug, study drug should be permanently discontinued and the participant managed according to local practice. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Study drug may be continued without dose interruption for a clinically nonsignificant Grade 3-4 laboratory abnormality (eg, CK elevation after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed) or a Grade 3-4 clinical event considered unrelated to study drug.

7.6.4. Management of Bone Evaluation

As there may be uncertainty surrounding the clinical significance and management of decreases in BMD, Gilead recommends that any participant who has a DXA scan that demonstrates a decrease from baseline of > 5% in the spine region or > 7% in the hip region be followed per local medical standards and as per the discretion of the investigator.

7.6.5. Management of Changes in Estimated Glomerular Filtration Rate

Estimated GFR, according to the Cockcroft-Gault formula, will be followed postbaseline during the study. All participants with eGFR < 60 mL/min must have serum creatinine and participant's weight measured again within 3 calendar days of receipt of results. If a participant has confirmed eGFR < 60 mL/min, the investigator should notify the medical monitor, evaluate potential causes, re-assess the potential risks and benefits of continued treatment in the study, and consider consultation with a qualified nephrologist.

7.6.6. Potential High-Risk Exposure

For participants who present after a high-risk sexual exposure, were non-adherent to study drug, and request PEP, investigators may discontinue the participant's study medication and provide PEP in accordance with local medical practice and/or guidelines. Participants who complete their PEP regimen and wish to continue on study may resume with study medication following the criteria as detailed in Section 6.8. Participants who present after a high-risk sexual exposure with reported good adherence to study drug do not require PEP.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To assess the rates of HIV-1 infection in MSM and 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 participants 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 DXA tests of hip and spine 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 RBP to creatinine ratio, urine beta-2-microglobulin 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 MSM and TGW who have sex with men who are administered daily F/TAF or F/TDF when all participants have 96 weeks of follow up after randomization
- To compare the general safety between the treatments

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8.1.2. Primary Endpoints

The primary endpoint will be the incidence of HIV-1 infection per 100 PY when all participants have a minimum follow up of 48 weeks and at least 50% of the participants have 96 weeks of follow up after randomization. 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 Ag/Ab or Ab test, confirmed by reactive HIV-1/HIV-2 differentiation assay), excluding HIV vaccinated participants, or

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

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

Please refer to Appendix 7 for more details.

8.1.3. Secondary Endpoints

The key (α-controlled) secondary endpoints in the blinded phase are (in the following order):

- The percent change from baseline in hip BMD at Week 48 in a subset of participants
- The percent change from baseline in spine BMD at Week 48 in a subset of participants
- Assessment of renal biomarkers at Week 48
  - percent change from baseline in urine beta-2-microglobulin to creatinine ratio
  - percent change from baseline in urine RBP to creatinine ratio
  - distribution of UP and UPCR categories
- The change from baseline in serum creatinine at Week 48

Other secondary endpoints include:

- The incidence of HIV-1 infection (as defined in Appendix 7) per 100 PY when all participants have 96 weeks of follow up after randomization
- The percent change from baseline in hip and spine BMD at Week 96 in the blinded phase in a subset of participants

- Assessment of renal biomarkers at Week 96 in the blinded phase
  - — percent change from baseline in urine beta-2-microglobulin to creatinine ratio
  - — percent change from baseline in urine RBP to creatinine ratio
  - — distribution of UP and UPCR categories
- The change from baseline in serum creatinine at Week 96 in the blinded phase
- The incidence of treatment-emergent AEs and laboratory toxicities

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8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Randomized Analysis Set

Participants that are randomized into the study will be included in this analysis set. This is the primary analysis set for by-participant listings.

8.2.1.2. Full Analysis Set (FAS)

The FAS will include all the participants who randomize and receive at least one dose of study drug. The FAS will exclude participants with major protocol violations (eg, HIV-1 positive at baseline). The FAS analysis set is the primary analysis set for the efficacy endpoints.

8.2.1.3. Per Protocol (PP) Analysis Set

The PP analysis set will include all participants who (1) randomize into the study, (2) receive at least one dose of study drug, and (3) have not committed any major protocol violation, including the violation of key entry criteria.

Participants meeting any of the following criteria will be excluded from the PP analysis set:

- HIV-1-positive at baseline
- Participants 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
- Nonadherence to study drug: participants with poor adherence rate for active study drug

8.2.1.4. Safety Analysis Set

The primary analysis set for safety analyses is defined as all participants who randomize in to the study and received at least one dose of study drug.

8.2.1.5. Hip DXA Analysis Set

The Hip DXA analysis set will include all participants who randomize and receive at least one dose of study drug, had nonmissing hip BMD value for the baseline visit and at least one postbaseline visit. Participants will be grouped according to the treatment they actually received.

8.2.1.6. Spine DXA Analysis Set

The Spine DXA analysis set will include all participants who randomize and receive at least one dose of study drug, and had nonmissing spine BMD value for the baseline visit and at least one postbaseline visit. Participants will be grouped according to the treatment they actually received.

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8.3. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, and age.

Baseline data will include a summary of body weight, height and body mass index, number of sexual partners in the last 3 months prior to screening, and number of acts of condomless anal intercourse.

8.4. Efficacy Analysis

8.4.1. Primary Analysis

The primary endpoint will be the incidence of HIV-1 infection per 100 PY (HIV-1 infection defined by the HIV Infection Endpoint Definition in Appendix 7). The timing of the primary analysis will occur when the last participant has a minimum of 48 weeks of follow up and at least 50% of the participants have 96 weeks of follow up after randomization. The primary analysis will consist of a noninferiority evaluation of F/TAF versus F/TDF, with respect to the HIV-1 infection rate in PY as determined by rate ratios. It will be concluded that F/TAF is non-inferior to F/TDF if the upper bound of the 95% CI of the rate ratio (F/TAF divided by F/TDF) is less than 1.62 using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the covariate.

If non-inferiority of F/TAF is established to F/TDF, and the upper bound of the 95% CI is less than 1, then superiority of F/TAF over F/TDF will be established.

8.4.2. Secondary Efficacy Analysis

A similar analysis to the primary analysis, when all participants have 96 weeks of follow up after randomization will be conducted. Similar incidence rates and CIs will be reported for the extended follow up time.

8.5. Safety Analysis

All safety analyses will be performed using the safety analysis set.

All safety data collected on or after the date that study medication was first dispensed up to the date of last dose of study medication plus 30 days will be summarized by treatment group. Data for the pretreatment and treatment-free follow-up period will be included in data listings.

8.5.1. Extent of Exposure

A participant's extent of exposure to study medication will be generated from the study medication administration data. Exposure data will be summarized by treatment group.

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration. Dosing information for individual participants will be listed.

8.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. Adverse events meeting the following criteria are defined as treatment-emergent AEs:

- Events with onset dates on or after the first dose date of study drug, and no later than 30 days after the study drug stop date, and/or
- Events that result in premature permanent study medication discontinuation

Summaries (number and percentage of participants) of treatment-emergent AEs (by SOC and PT) will be provided. Additional summaries will include summaries for AEs by grade, investigator's assessment of relationship to study medication, and effect on study drug dosing.

8.5.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Absolute values and changes from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 5).

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time postbaseline up to the date of last dose of study medication plus 30 days, will be summarized. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent. The maximum toxicity grade will be summarized by laboratory parameter.

Laboratory abnormalities that occur before the first dose of study medication or after the participant has been discontinued from treatment plus 30 days will be included in a data listing.

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8.5.6. Other Safety Evaluations

Weight will be summarized by visit.

8.6. Statistical Testing Procedure

The primary hypothesis of non-inferiority of F/TAF relative to F/TDF, with respect to the incidence of HIV-1 infection rate per 100 PY will be tested first. Non-inferiority test will be performed at one-sided, 0.025 alpha level. Multiplicity adjustments for safety endpoints will be performed at Week 48 of the blinded phase with a fallback procedure {Wiens 2005} in the sequential order given below with pre-specified two-sided alpha levels:

a) Hip BMD (alpha = 0.02)

b) Spine BMD (alpha = 0.01)

c) Renal biomarkers (alpha = 0.02)

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8.8. Sample Size

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 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 are assumed.

The non-inferiority margin of 1.62 and HIV-1 infection rate of 1.44 per 100 PY are based on an equal weighting approach using 3 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 8-1 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 3 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 3 studies gives relatively more weight to the 2 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 participants in the proposed study. IPREX, the largest and earliest of these 3 studies, was conducted when the effectiveness of F/TDF for PrEP was not established; thus, patients 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, and likely contributed to the much higher adherence rate reported.

Table 8-1. 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]	Enrollment
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}; Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD) from {McCormack 2015}

* The pooled incidence rate for placebo and F/TDF, based on equal weighting of 3 studies are within {} which are used for estimating the rate ratio and its 95% CI.

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For the percent change in renal biomarkers of urine beta 2-microglobulin to creatinine ratio and urine RBP 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 participant 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 Gilead HIV Studies GS-US-292-0104/GS-US-292-0111 (E/C/F/TAF vs E/C/F/TDF) and HBV Studies GS-US-320-0108/GS-US-320-0110 (TAF vs TDF). To be conservative, the smaller effect size from 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 patients take study drug daily, if patients 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.

8.9. Data Monitoring Committee

An independent data monitoring committee (IDMC) will be convened to primarily evaluate the safety of the treatments in this population. There are no a priori plans to stop for efficacy or futility with formal boundaries. At a minimum, the IDMC will include 2 clinicians (including a chairperson), a biostatistician, a prevention expert, and a community member. The initial evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 24 (or prematurely discontinued from the study drug) or (2) after 50 HIV-1 infection events have been reported, whichever occurs earlier. The second evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 48 (or prematurely discontinued from the study drug) or (2) after 100 HIV-1 infection events have been reported, whichever occurs earlier. The third evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 72 (or prematurely discontinued from the study drug) or (2) after 150 HIV-1 infection events have been reported, whichever occurs earlier. Other specifics regarding roles and responsibilities will be described in the IDMC charter.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. These standards are consistent with the EU Clinical Trials Directive 2001/20/EC and GCP Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of GCP, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study participant activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC or local requirements.

9.1.4. Confidentiality

The investigator must assure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only participant initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions
NOTE: The investigator must keep a screening log showing codes, names, and addresses for all participants screened and for all participants enrolled in the study. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and
(2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, case report form (CRF) and query forms, IRB/IEC and governmental approval with correspondence, ICFs, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification (name, date of birth, gender)
- Documentation that participant meets eligibility criteria, ie history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date, and including causality and severity)
- Concomitant medication (including start and end date, dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture (EDC) system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the case report form Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

The study monitor will provide instructions for return to the designated disposal site. If return is not possible, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review study drug supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met: the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any participant records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the participants' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

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

GS-US-412-2055, Amendment 7, 19 October 2021

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

[See appended electronic signature]	*[See appended electronic signature]*
PPD PPD (Printed)	Signature
Date	

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Prot-GS-US-412-2055_amd-7

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	20-Oct-2021 16:10:40

Appendix 2. 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 Up to OL Week 96[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[ab] (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)[ab]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample for Gonorrhea and Chlamydia	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rapid HIV-1 Ag/Ab Test (In-Clinic)[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 Ab/Ag[q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 RNA by PCR[r]	X	X[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Screening	Day 1	Double-Blind Treatment End of Week[a]									Post Week 96	Open-Label Treatment End of Week[c]							
			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 Up to OL Week 96[d]	30-Day Follow-up[e]	ESDD[f]
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
CCI																				
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[ac]	X[ac]		X		X	X[ac]		
Hepatitis C Testing (HCV Ab)	X						X				X	X[ad]	X[ad]				X	X[ad]		
Estimated GFR	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																				
CCI																				
CCI																				
Plasma Storage Sample[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CASI Questionnaire[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Randomization in IXRS		X																		
Risk Reduction/ Adherence Counseling	X[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Study Procedure	Screening	Day 1	Double-Blind Treatment End of Week[a] 4	12	24	36	48	60	72	84	96	Post Week 96 Every 12 Weeks	Open-Label Treatment End of Week[c] end of blinded treatment phase visit[b]	12	24	36	48	Every 12 Weeks Up to OL Week 96[d]	30-Day Follow-up[e]	ESDD[f]
CCI																				
Study Drug Dispensation and Accountability		X[y]	X	X	X	X	X	X	X	X	X	X	X[z]	X	X	X	X	X		X[aa]
CD4, CD8, and CD4/CD8 (for participants who acquire HIV)			Performed at all visits after HIV infection.																X	X
Latent and Active Reservoir assessment (for participants who acquire HIV)			Performed for participants who acquire HIV 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.																	
T cell response and phenotype (for participants who acquire HIV)			Performed for participants who acquire HIV 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.																	
Viral Sequence Diversity assessment (for participants who acquire HIV)			Performed for participants who acquire HIV only. Performed at first study visit after HIV infection and at regularly scheduled study visit 24 weeks after HIV infection only.																	
Inflammatory/Immune Activation Biomarkers (for participants who acquire HIV)			Performed for participants who acquire HIV 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.																	

Ab = antibody; Ag = antigen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CASI = Computer-Assisted Self-Interview; CD = cluster determinant; CCI CCI ; ESDD = early study drug discontinuation; GFR = glomerular filtration rate; GGT = gamma glutamyl transferase; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; IXRS = interactive voice/web response system; LDH = lactate dehydrogenase; OL = open-label; CCI PCR = polymerase chain reaction; PK = pharmacokinetic; STI = sexually transmitted infection; ULN = upper limit of normal

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 participants 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 Participants will continue study visits every 12 weeks in the OL phase up to OL Week 96 (not including OL Week 96). From OL Week 96, refer to Appendix 3.

e For 30-Day Follow-up visits conducted prior to OL Week 96, must be completed 30 days after discontinuing study drug. All participants 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 For Early Study Drug Discontinuation Visits conducted prior to OL Week 96, visit to occur within 72 hours of last dose of study drug. Participants 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 participants with total amylase > 1.5 × ULN).

i Complete blood count (CBC) with differential and platelet count

[redacted]

k Local STI testing for syphilis.

[redacted]

m For possible PK, virology, and/or safety testing

n Computer-assisted self-interview (CASI)

o If Day 1 is completed > 7 days after the screening visit

p Fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test may be used. If fourth generation rapid HIV-1 Ag/Ab or third generation rapid HIV-1 Ab test is positive, a retest will be completed. At screening or Day 1, if rapid retest is positive the participant 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 participant 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 participant 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, participant 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 participants 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, participant will discontinue study drug immediately and should return for an ESDD visit within 72 hours. The participant 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 participants who show symptoms consistent with acute HIV-1 infection regardless of the results of the rapid tests.

[redacted]

u Only risk reduction counseling at screening

[redacted]

y Only study drug dispensation at Day 1

z OL drug dispensation (all eligible participants will receive F/TAF)

aa No study drug dispensed.

ab Swabs may be self-administered by the participant at the discretion of the investigator.

ac 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 > 24 weeks from prior testing.

ad 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 3. Study Procedures Table (OL Week 96 and beyond)

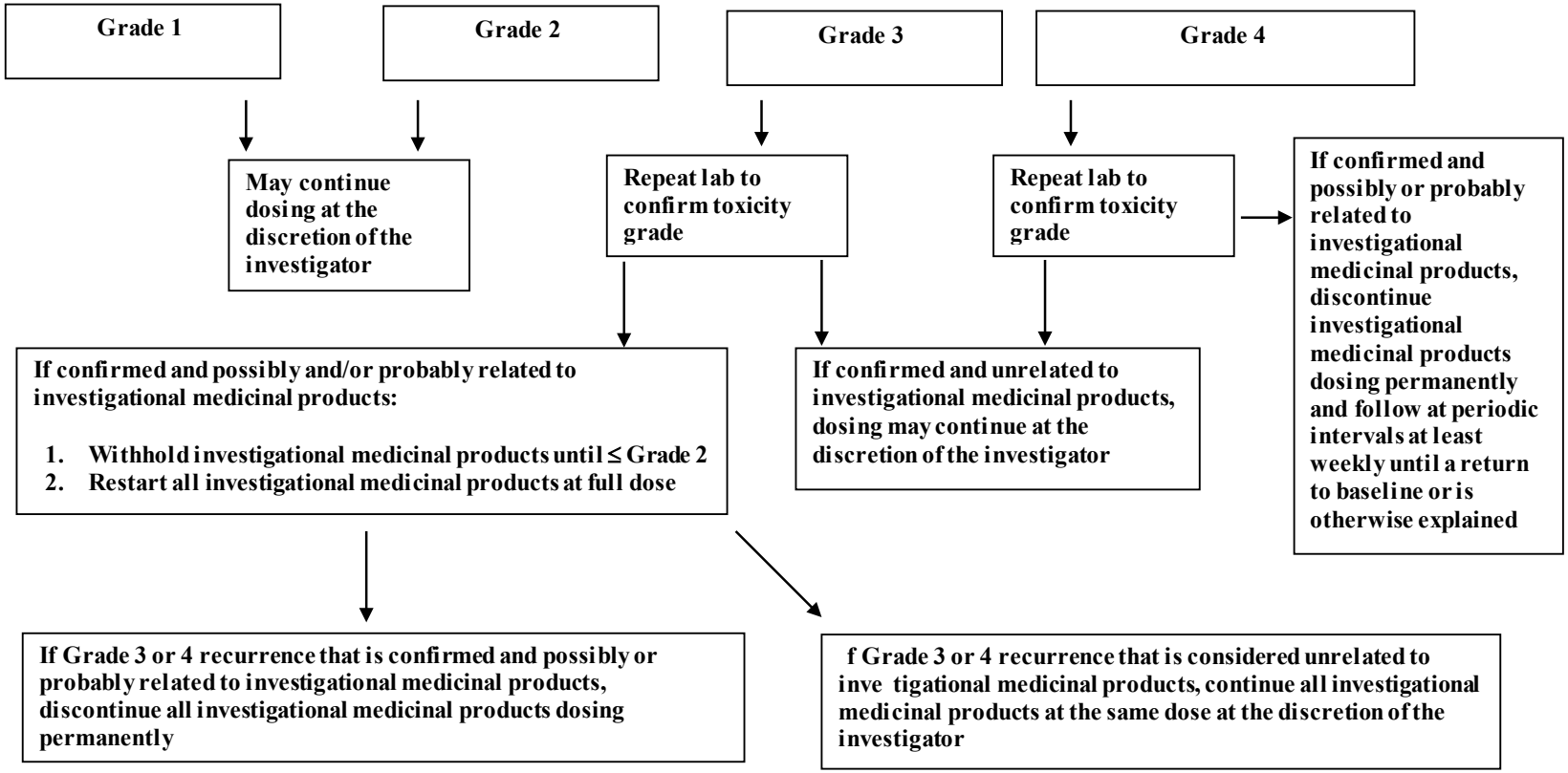
	Open-Label Extension Treatment End of Week[a]		
Study Procedure	**OL Week 96 and Every 12 Weeks until OL Week 408[b]**	**30-Day Follow-up[c]**	**ESDD[d]**
Concomitant Medications	X	X	X
Adverse Events	X	X	X
Targeted Physical Exam[f]	X[f]	X	X
Vital Signs[e]	X[e]	X	X
Weight[f]	X[f]	X	X
Genital, Rectal, and Pharyngeal Examination for STIs as appropriate	X	X	X
Pharyngeal Swab for Gonorrhea and Chlamydia (Local Laboratory)[g]	X	X	X
Rectal Swab for Gonorrhea and Chlamydia (Local Laboratory)[g]	X	X	X
Urine Sample for Gonorrhea and Chlamydia	X	X	X
Rapid HIV-1 Ag/Ab Test (In-Clinic)[h]	X	X	X
HIV-1 Ab/Ag[i]	X	X	X
HIV-1 RNA by PCR[j]	X	X	X
Blood Sample for Chemistry Profile[k]	X[k]	X	X
CCI			
Blood Sample for Syphilis Testing (Local Laboratory)	X	X	X
Hepatitis B Testing (HBsAg/HBsAb/HBcAb)	X[m]		
Hepatitis C Testing (HCV Ab)	X[n]		
Estimated GFR	X[o]	X	X

Study Procedure	Open-Label Extension Treatment End of Week[a]		
	OL Week 96 and Every 12 Weeks until OL Week 408[b]	30-Day Follow-up[c]	ESDD[d]
CCI [redacted]			
Risk Reduction/Adherence Counseling	X		
Study Drug Dispensation and Accountability	X		X[q]
CD4, CD8, and CD4/CD8 cell count (for participants who acquire HIV)		X	X

Ab = antibody; Ag = antigen; BUN = blood urea nitrogen; CD4 = cluster determinant 4; CD8 = cluster determinant 8; DBS = dried blood spot; ESDD = early study drug discontinuation; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; OL = open label; PCR = polymerase chain reaction; STI = sexually transmitted infection

a Visit windows are ± 14 days of the protocol-specified date, based on the end of blinded treatment phase visit, through the Open Label Extension phase visit, unless otherwise specified.
b Participants will continue study visits in the OL extension phase every 12 weeks until OL Week 408.
c Must be completed 30 days after discontinuing study drug. All participants 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.
d Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug.
e Vital signs measurement including blood pressure, pulse, respiration rate, and temperature, every 24 weeks
f Every 24 weeks
g Swabs may be self-administered by the participant at the discretion of the investigator.
h At a minimum, fourth generation rapid HIV-1 Ab/Ag or third generation rapid HIV-1 Ab test may be used. If fourth generation rapid HIV-1 Ag/Ab or third generation rapid HIV-1 Ab test is positive, retest will be completed. If rapid retest is positive, then HIV-1 RNA by PCR test and sample collection for possible genotypic testing will be completed.
i If HIV-1 Ab/Ag is positive, then HIV-1 RNA by PCR test and sample collection for possible genotypic testing will be completed.
j HIV-1 RNA by PCR and sample collection for possible genotypic resistance testing will be completed for any participants 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, participant will discontinue study drug immediately and should return for an ESDD visit within 72 hours. The participant 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.
k Chemistry profile: bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, sodium **every 24 weeks.**
CCI [redacted]
m Hepatitis B testing (HBsAg, HBsAb, HBcAb) to be completed **every 48 weeks.**
n Hepatitis C testing to be completed every 48 weeks.
o Estimated GFR every **24 weeks**
CCI [redacted]
q No study drug dispensed.

Appendix 4. Management of Clinical and Laboratory Adverse Events



Appendix 5. Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months[#]**	1000 to 1300/mm^3	750 to < 1000/mm^3	500 to < 750/mm^3	< 500/mm^3
	1.00 to 1.30 GI/L	0.75 to < 1.00 GI/L	0.50 to < 0.75 GI/L	< 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3	1,500 to < 2,000/mm^3	1000 to < 1,500/mm^3	< 1000/mm^3
	2.00 GI/L to 2.50 GI/L	1.50 to < 2.00 GI/L	1.00 to < 1.50 GI/L	< 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL	75 to < 100 mg/dL	50 to < 75 mg/dL	< 50 mg/dL
	1.00 to 2.00 g/L	0.75 to < 1.00 g/L	0.50 to < 0.75 g/L	< 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL	> 600 mg/dL	—	—
	> ULN to 6.0 g/L	> 6.0 g/L	—	—
Fibrin Split Product	20 to 40 µg/mL	> 40 to 50 µg/mL	> 50 to 60 µg/mL	> 60 µg/mL
	20 to 40 mg/L	> 40 to 50 mg/L	> 50 to 60 mg/L	> 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 3.0 × ULN	> 3.0 × ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

An overlap between the Grade 1 scale and the Lab's normal range for absolute neutrophils may result for pediatric participants. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to < LLN mEq/L	125 to < 130 mEq/L	121 to < 125 mEq/L	< 121 mEq/L
	130 to < LLN mmol/L	125 to < 130 mmol/L	121 to < 125 mmol/L	< 121 mmol/L
Hypernatremia	> ULN to 150 mEq/L	> 150 to 154 mEq/L	> 154 to 159 mEq/L	> 159 mEq/L
	> ULN to 150 mmol/L	> 150 to 154 mmol/L	> 154 to 159 mmol/L	> 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to < LLN mEq/L	2.5 to < 3.0 mEq/L	2.0 to < 2.5 mEq/L	< 2.0 mEq/L
	3.0 to < LLN mmol/L	2.5 to < 3.0 mmol/L	2.0 to < 2.5 mmol/L	< 2.0 mmol/L
Infant <1 Year	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	> ULN to 6.0 mEq/L > ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL	> 160 to 250 mg/dL	> 250 to 500 mg/dL	> 500 mg/dL
	6.42 to 8.91 mmol/L	> 8.91 to 13.90 mmol/L	> 13.90 to 27.79 mmol/L	> 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	> 125 to 250 mg/dL > 6.96 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 < LLN mg/dL 1.94 to < LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to < 7.8 mg/dL 1.74 to <1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	> ULN to 11.5 mg/dL	> 11.5 to 12.5 mg/dL	> 12.5 to 13.5 mg/dL	> 13.5 mg/dL
	> ULN to 2.88 mmol/L	> 2.88 to 3.13 mmol/L	> 3.13 to 3.38 mmol/L	> 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN	2.5 to < 3.0 mg/dL	2.0 to < 2.5 mg/dL	< 2.0 mg/dL
	0.74 mmol/L to < LLN	0.62 to < 0.74 mmol/L	0.49 to < 0.62 mmol/L	< 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL	> 6.0 to 6.5 mg/dL	> 6.5 to 7.0 mg/dL	> 7.0 mg/dL
	> ULN to 1.50 mmol/L	> 1.50 to 1.63 mmol/L	> 1.63 to 1.75 mmol/L	> 1.75 mmol/L
Hypomagnesemia	1.40 to < LLN mg/dL 1.2 to < LLN mEq/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L	< 0.67 mg/dL < 0.6 mEq/L
	0.58 to < LLN mmol/L	0.43 to < 0.58 mmol/L	0.28 to < 0.43 mmol/L	< 0.28 mmol/L
Hypophosphatemia Adult and Pediatric > 14 Years	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pediatric 1 Year–14 Years	3.0 to < LLN mg/dL 0.96 to < LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to < LLN mg/dL 1.12 to < LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	> ULN to 10.0 mg/dL	> 10.0 to 12.0 mg/dL	> 12.0 to 15.0 mg/dL	> 15.0 mg/dL
	> ULN to 597 µmol/L	> 597 to 716 µmol/L	> 716 to 895 µmol/L	> 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dL to < LLN- 57 µmol to < LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN	11.0 to < 16.0 mEq/L	8.0 to < 11.0 mEq/L	< 8.0 mEq/L
	16.0 mmol/L to < LLN	11.0 to < 16.0 mmol/L	8.0 to < 11.0 mmol/L	< 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/L to < LLN	8.0 to < 11.0 mEq/L	< 8.0 mEq/L
		11.0 mmol/L to < LLN	8.0 to < 11.0 mmol/L	< 8.0 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) **Adult**	130 to 160 mg/dL	>160 to 190 mg/dL	> 190 mg/dL	NA
	3.35 to 4.15 mmol/L	> 4.15 to 4.92 mmol/L	> 4.92 mmol/L	
LDL (Fasting) **Pediatric >2 to <18 years**	110 to 130 mg/dL	> 130 to 190 mg/dL	> 190 mg/dL	NA
	2.84 to 3.37 mmol/L	> 3.37 to 4.92 mmol/L	> 4.92 mmol/L	
Hypercholesterolemia (Fasting)	200 to 239 mg/dL	> 239 to 300 mg/dL	> 300 mg/dL	NA
	5.16 to 6.19 mmol/L	> 6.19 to 7.77 mmol/L	> 7.77 mmol/L	
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male participants > 70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatrics <16 years**	-	2.0 to < LLN g/dL 20 to < LLN g/L	< 2.0 g/dL < 20 g/L	NA
≥ 16 years	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females	> ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection				
Adult and Pediatric ≥ 10 Years	200 to 999 mg/24 h	> 999 to 1999 mg/24 h	> 1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	> 499 to 799 mg/m^2/24 h	> 799 to 1000 mg/m^2/24 h	> 1000 mg/m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by the central laboratory (Prior to OL Week 96); however, for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (eg, the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
			with nonurgent intervention indicated	
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional- symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Central nervous system (CNS) Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental	Moderate developmental delay, either motor or cognitive, as determined by comparison with a	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental	Developmental regression, either motor or cognitive, as determined by comparison with a developmental

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
	screening tool appropriate for the setting	developmental screening tool appropriate for the setting	screening tool appropriate for the setting	screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (preexisting) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of preexisting seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

ADD = attention deficit disorder.

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

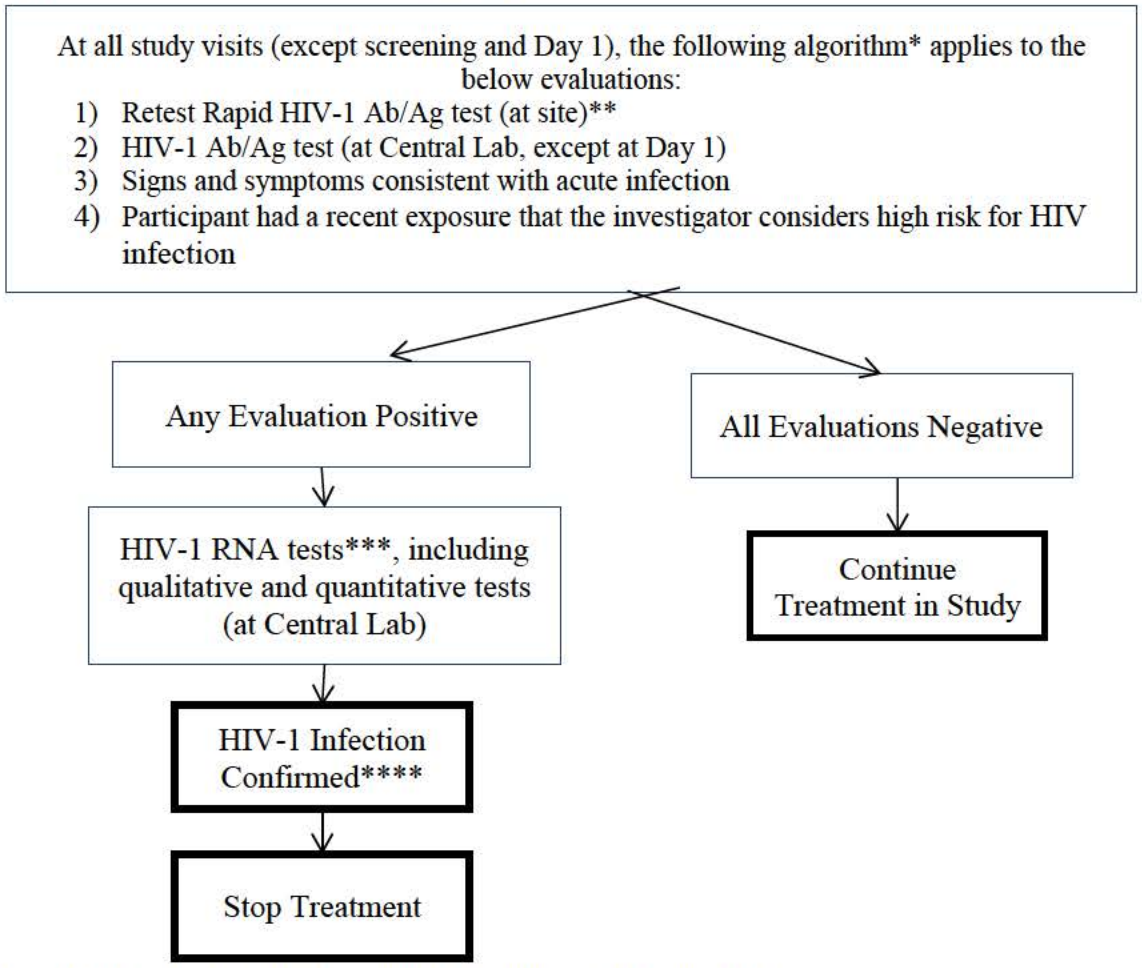
ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 6. HIV Testing Algorithm



* The HIV testing algorithm does not apply to participants who acquire HIV.

** If the result for rapid testing is positive, a retest will be completed. If the retest rapid is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.

*** May continue study drug, or may begin a full HIV treatment regimen until HIV-1 diagnosis is confirmed, at investigator discretion {Center for Disease Control and Prevention (CDC) 2018}.

**** HIV infection as defined per Appendix 7

Appendix 7. HIV Infection Endpoint Definition

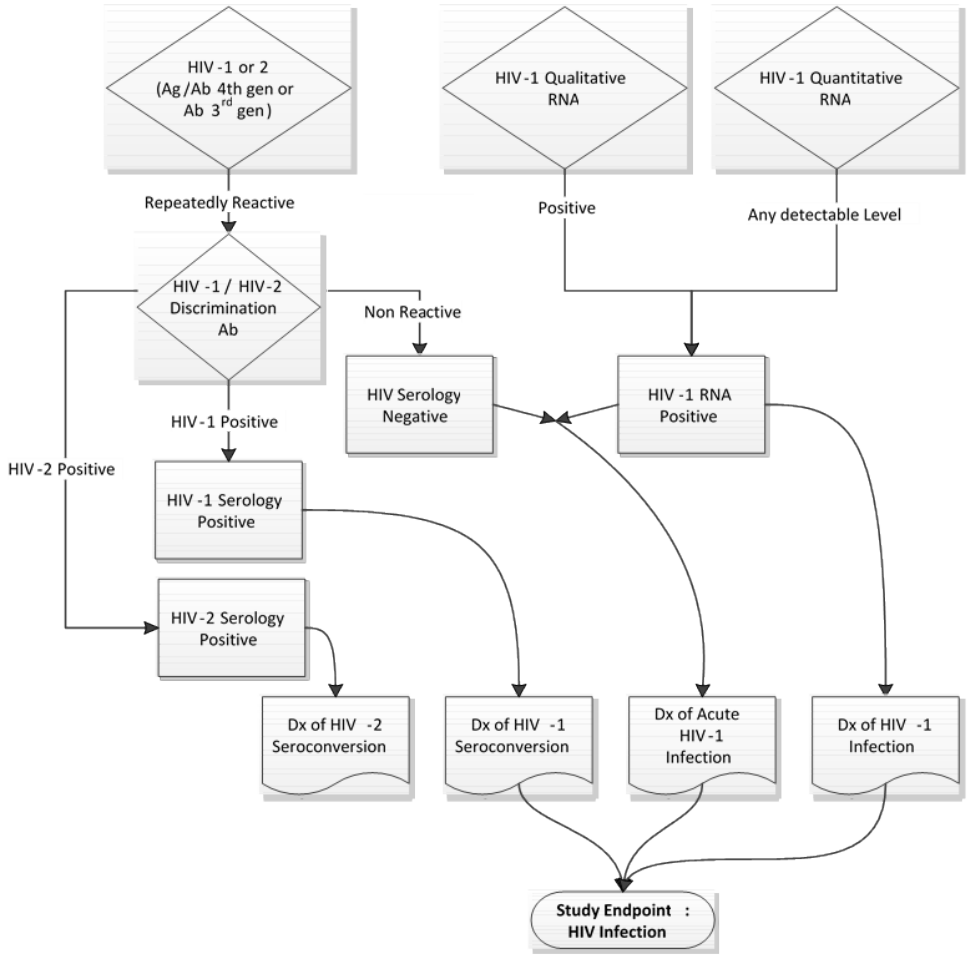
HIV-1 infection is defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab:

1) Serologic evidence of seroconversion (reactive screening HIV Ag/Ab or Antibody test, confirmed by reactive HIV-1/HIV-2 differentiation assay), excluding HIV vaccinated participants, or

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

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

Please refer to the flowchart below which focuses on contributions from the central laboratory and provides a general assessment of contributing HIV tests performed by the central laboratory.



Appendix 8. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to participants and sites:

   a) Participants may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any participant visits.

   Mitigation plan: Study drug supplies may be provided to the participant from the site without a clinic visit, once it is confirmed that the HIV test result is negative and the participant may safely continue on study drug as determined by the principal investigator (PI). A virtual study visit, via phone or video conferencing, must be performed prior to remote study drug resupply. Prior to the virtual visit, the PI or qualified designee should contact the participant to obtain verbal consent from the participant to ship and perform the home rapid HIV test or arrange for the participant to attend a local lab/facility for HIV testing. Participant should be given clear instructions on how to perform the HIV test. The date and time that consent was obtained must be documented in the participant's medical records. The PI or qualified designee will then perform the virtual visit, including review of the HIV test result, within the protocol target visit window dates whenever possible. The calls should be documented in the source documents at the site and relevant information entered in EDC. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments. The HIV test result must be obtained prior to dispensing and/or shipping of the study drug to the participant. A qualified courier may be utilized to ship the study drug from sites to study participants if permitted by local ethics committee (EC)/institutional review boards (IRB)/Regulatory Authority as applicable and with sponsor's approval.

   b) Shipments of study drug could be delayed because of transportation issues. Without study drug participant would not be able to stay on the study drug as planned per protocol.

   Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

   c) Stopping or interrupting study drug may lead to resistance to study drug components.

   Mitigation plan: Participant may stop study drug per protocol and go on a preapproved drug-holiday. Drug holidays are approved by the Gilead medical monitor. Following a drug holiday or drug interruption for more than 14 days, protocol Section 6.8 must be followed when study drug is re-started. Drug holidays will not be approved after OL Week 96.

2) Participant safety monitoring and follow-up:

a) Participants may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

Mitigation plan: For participants who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the PI or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the participant within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

i) Confirm if participant has experienced any adverse events (AEs/serious adverse events [SAEs]/special situations) and follow up on any unresolved AE/SAEs.

ii) Review current list of concomitant medications and document any new concomitant medications.

iii) Confirm participants study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (1).

iv) Remind participant to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Participants may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central lab analyses.

Mitigation plan: A local lab may be utilized per PI discretion to monitor the participant safety until the participant can return for their regular follow up per protocol. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly.

A) HIV testing must occur every 3 months per PrEP standard of care. Per protocol, HIV testing is performed locally by site. If a participant is unable to attend a study visit, participant may either utilize a local laboratory/facility/resource to perform the HIV test or may perform home HIV testing prior to receiving study drug in agreement with CDC guidance.

B) If study drug was shipped without HIV testing and no subsequent rapid HIV test result is available, site should arrange for HIV testing to be performed immediately either via an onsite visit or via remote testing (home or local lab) and the result should be provided to the site. If it has been more than 6 months since the last rapid HIV test, participant should attend site for an on-site fourth or fifth generation Ab/Ag test or should have this test performed at a local lab and if this is not possible discuss with the medical monitor regarding study continuation. Information on study-drug adherence and site's risk / benefit assessment must be documented in the source notes and in EDC (and the IPD if applicable). Where

HIV testing was not completed, the medical monitor should be provided the participant risk-benefit assessment for review.

C) If participants are unable to go to site for more than 6 months, safety labs should be sent to the central lab where possible. If labs cannot be sent to the central lab, the participant may have safety labs performed locally, which should include at minimum a serum creatinine level to assess renal function and STI testing, in accordance with PrEP standard of care.

c) Participants may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented in the source and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic. Home HIV testing or HIV testing at a local lab will be recorded as a protocol deviation.

i) If ESDD is performed remotely, where possible, the safety follow-up visit should be completed on-site including all required assessments to ensure that we are not transferring participants to off-study PrEP services who have HIV or should not be on PrEP for safety reasons. If the CASI questionnaire (prior to OL Week 96) and DXA scan was not completed, where possible site should schedule both at the safety-follow-up visit (DXA only for applicable sites).

b) Monitors may be unable to carry out source data review (SDR) or source data verification (SDV), or study drug accountability or assess protocol and GCP compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   a) There may be an increased amount of missing data due to participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical trial data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with Regulatory Authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of study drug in study participants remains unchanged.