CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed on Regimens containing ABC/3TC	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 9440	
IND Number:	111851	
EudraCT Number:	2015-000871-28	
Clinical Trials.gov Identifier:	*Not Available*	
Indication:	HIV-1 Infection	
Protocol ID:	GS-US-311-1717	
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 3b, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed on Regimens containing ABC/3TC
IND Number:	111851
EudraCT Number:	2015-000871-28
Clinical Trials.gov Identifier:	*Not Available*
Study Centers Planned:	Approximately 100 centers in Europe and North America
Objectives:	The primary objective is: • To evaluate the efficacy of switching ABC/3TC to F/TAF versus maintaining ABC/3TC in HIV-1 infected subjects who are virologically suppressed on regimens containing ABC/3TC as determined by the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 The secondary objectives are: • To evaluate the efficacy, safety and tolerability of two regimens through Week 48 and Week 96 • To evaluate the bone safety of two regimens as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Week 48 and Week 96
Study Design:	Randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of switching ABC/3TC fixed-dose combination (FDC) tablet to F/TAF FDC tablet versus continuing ABC/3TC in HIV-1 infected subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen containing ABC/3TC for ≥ 6 consecutive months prior to screening. All subjects will be randomized, in a blinded fashion, in a 1:1 ratio to either switch from ABC/3TC to F/TAF + placebo-to-match ABC/3TC or maintain the ABC/3TC + placebo-to-match F/TAF while continuing the protocol allowed third agent (as prescribed by the

	Investigator) in their antiretroviral (ARV) regimen. Subjects who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to one of the following two treatment arms: **Treatment Arm 1**: F/TAF + Placebo-to-match ABC/3TC; third antiretroviral agent remains the same (n = 250) **Treatment Arm 2**: ABC/3TC + Placebo-to-match F/TAF; third antiretroviral agent remains the same (n = 250) Since different antiretroviral third agents require different doses of TAF, randomization will be stratified by the third agents: boosted protease inhibitors vs. other agents (see below for protocol allowed third agents).
Number of Subjects Planned:	Approximately 500 subjects total with approximately 250 subjects each in Treatment Arm 1 and Treatment Arm 2.
Target Population:	HIV-1 infected adult subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen containing ABC/3TC for ≥ 6 consecutive months prior to screening.
Duration of Treatment:	Subjects will be treated for 96 weeks in the randomized phase. After Week 96, subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments have been unblinded. After unblinding, in countries where F/TAF FDC is not commercially available, subjects will be given the option to receive the open-label F/TAF FDC and attend study visits every 12 weeks until it becomes commercially available, or until Gilead Sciences terminates the study in that country.
Diagnosis and Main Eligibility Criteria:	HIV-1 infected adult subjects who meet the following criteria will be given the option to participate in the study: • Currently receiving an antiretroviral regimen containing ABC/3TC in combination with one third agent for ≥ 6 consecutive months prior to screening • Plasma HIV-1 RNA < 50 copies/mL for ≥ 6 months preceding the screening visit (measured at least twice using the same assay) and not experienced two consecutive HIV-1 RNA measurements above detectable levels after achieving a confirmed (two consecutive) HIV-1 RNA measurement below detectable levels on the current regimen in the past year. Plasma HIV-1 RNA should be < 50 copies/mL at the screening visit • Estimated glomerular filtration rate ≥ 50 mL/min (Cockcroft - Gault formula)

Study Procedures/ Frequency:	After screening, eligible subjects will be randomized to Treatment Arm 1 or 2 and treated for 96 weeks. Following the Screening and Day 1 visits, subjects will return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Unblinding Visit. Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count, and complete or symptom directed physical examinations will be performed at the Screening, Day 1, and all subsequent study visits. For all subjects, dual energy x-ray absorptiometry (DXA) scans will be performed prior to study drug administration at Day 1 and every 24 weeks until Week 96, at Unblinding Visit and at Early Study Drug Discontinuation (ESDD), if > 12 weeks since last scan. Scans will cover the spine and hip to measure changes in bone mineral density. Analyzed DXA scans will be provided to study sites when available. Blood and urine for selected evaluations of renal tubular function and bone turnover will be collected at Day 1, Weeks 4, 12, 24, 48, 72, 96 and ESDD (if applicable). In addition, blood will be collected and stored at Day 1, Weeks 4, 12, 24, 48, 72, and 96 and ESDD (if applicable) for possible evaluation of inflammation and immune activation, including cystatin-C, IL-6, hs-CRP, d-dimer, sCD14, and sCD163. Platelet function evaluations will also be assessed, including soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand. A single PK blood sample will be collected any time pre or post-dose at Weeks 8, 12, 24, and 36. At Weeks 4 and 48 the single PK blood sample will be collected between 15 minutes and 4 hours post-dose. A whole blood sample will be collected at Week 4 visit for assessment of archived provirus in peripheral blood mononuclear cells (PBMCs). In a subset of patients, platelet function will be assessed at Day 1 visit, Weeks 4 and 12, and the Early Study Drug Discontinuation Visit (if applicable). Subjects who complete the study through the Unblinding Visit and do not wish to continue to participate will be required to return to the clinic 30 days after the completion of the study drug for a 30-Day Follow-up Visit. Adverse events and concomitant medications will be assessed at each visit.

Test Product, Dose, and Mode of Administration:

F/TAF FDC tablet administered orally once a day (QD).

Recommended F/TAF dose by co-administered third agent:

Treatment Arm 1	Allowed Third Agents
F/TAF (200/10 mg)	LPV/r, ATV+RTV, ATV+COBI (or ATV/COBI FDC), DRV+RTV, DRV+COBI (or DRV/COBI FDC)
F/TAF (200/25 mg)	EFV, RPV, RAL, DTG, MVC, NVP

Reference Therapy, Dose, and Mode of Administration:

ABC/3TC (600/300 mg) FDC tablet administered orally once a day (QD)

Criteria for Evaluation:

Safety:

Adverse events, clinical laboratory tests (including selected evaluations of renal tubular function, bone turnover, and inflammation), and DXA to evaluate the safety and tolerability of the two regimens

Efficacy:

The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the Food and Drug Administration (FDA) snapshot algorithm.

Other secondary endpoints include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 96 as defined by the FDA snapshot algorithm
- The percent change from baseline in hip and spine BMD at Week 48 and Week 96

Pharmacokinetics:

The PK of individual analytes may be explored.

Statistical Methods:

The primary analysis will consist of a non-inferiority evaluation of switching to F/TAF versus maintaining ABC/3TC, with respect to the proportion of subjects with HIV-1 RNA less than 50 copies/mL at Week 48 (as defined by the FDA snapshot algorithm). It will be concluded that F/TAF is non-inferior to the ABC/3TC if the lower bound of the two-sided 95% confidence interval of the difference between treatment arms (F/TAF – ABC/3TC) in the response rate is greater than −10% (i.e. a margin of 10% is applied to non- inferiority assessment). The 95% confidence interval will be constructed using the normal approximation method based on stratified Mantel-Haenszel proportions, where the stratification factor is the third agents (boosted protease inhibitors vs. other agents).

	The secondary analysis evaluating switching to F/TAF versus maintaining ABC/3TC, with respect to the percent change from baseline in hip and spine BMD will be conducted using Analysis of Variance (ANOVA), including the third agent stratum as a fixed effect. The adverse events and clinical laboratory data will be summarized using descriptive statistics.
Sample Size:	A total of approximately 500 HIV-1 infected subjects, randomized in a 1:1 ratio to two arms (250 subjects per arm), achieves at least 90% power to detect a non-inferiority margin of 10% in Week 48 response rate (HIV-1 RNA < 50 copies/mL as defined by the FDA snapshot algorithm) difference between the two groups. For sample size and power computation, it is assumed that both treatment arms have a response rate of 0.87, that a non-inferiority margin is 0.10, and that the significance level of the test is at a one-sided 0.025 level.

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

° C	degrees Celsius
° F	degrees Fahrenheit
3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ANOVA	analysis of variance
ARV	antiretroviral
AST	aspartate aminotransferase
ATR	Atripla®; EFV/FTC/TDF
ATV	atazanavir
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last measurable concentration
AUC_{tau}	area under the plasma concentration-time curve at the end of the dosing interval
AV	atrioventricular
BMD	bone mineral density
BUN	blood urea nitrogen
CBC	complete blood count
CK	creatine kinase
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CNS	central nervous system
COBI, /co	cobicistat
CPK	creatine phosphokinase
CRF	case report form(s)
CRO	contract (or clinical) research organization
CSR	clinical study report
CTX	type 1 collagen crosslinked C-telopeptide
CYP	cytochrome P450
DDI	drug-drug interaction
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

DRV	darunavir
DSPH	Drug Safety and Public Health
DTG	dolutegravir
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
EFV	efavirenz
EVG	elvitegravir
E/C/F/TDF	elvitegravir (EVG) 150 mg/cobicistat (COBI) 150 mg/emtricitabine (FTC) 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg single tablet regimen
E/C/F/TAF	elvitegravir (EVG) 150 mg/cobicistat (COBI) 150 mg/emtricitabine (FTC) 200 mg/tenofovir alafenamide (TAF) 10 mg single tablet regimen
ESDD	early study drug discontinuation
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination
FTC	emtricitabine
F/TAF	emtricitabine/tenofovir alafenamide
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practice (Guidelines)
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
GS-7340	tenofovir alafenamide, TAF, L-Alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]/ phenoxyphosphinyl]-, 1-methylethyl ester
HAART	highly active antiretroviral therapy
HBsAg	hepatitis B virus surface antigen serology
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus serology
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HSP	hysterosalpingogram
IB	investigator's brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
INSTI	integrase strand transfer inhibitor
IMP	Investigational Medicinal Product
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
KS	Kaposi's sarcoma
LDH	lactate dehydrogenase
LLN	lower limit of the normal range
LLT	low-level term
LPV	lopinavir
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
Min	minute
mmHg	millimeters mercury
MVC	maraviroc
NNRTI	non-nucleoside reverse transcriptase inhibitor
N[t]RTI	nucleos(t)ide reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
P1NP	procollagen Type 1 N-terminal propeptide
PBMCs	peripheral blood mononuclear cells
PI	protease inhibitor
PK	pharmacokinetic
PT	preferred term
QD	once daily
RAL	raltegravir
RBC	Red blood cells
RNA	ribonucleic acid
RPV	rilpivirine
RTV, /r	ritonavir
SADR	serious adverse drug reaction
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure
STB	Stribild®, EVG/COBI/FTC/TDF (E/C/F/TDF) STR

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	tenofovir alafenamide (GS-7340)
TAF fumarate	tenofovir alafenamide fumarate (GS-7340-03)
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate (TFVpp)
T_{max}	the time (observed time point) of Cmax
UGT	uridine glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
WBC	white blood cells
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the serum, plasma concentration of drug versus time curve

1. INTRODUCTION

1.1. Background

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 35 million people infected worldwide {27071}. Standard of care for the treatment of HIV-1 infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression.

The success of potent and well-tolerated ART means that morbidity and mortality in the HIV-infected population is increasingly driven by non-AIDS–associated comorbidities. Clinical attention has become more focused on optimizing tolerability, long-term safety, and adherence {29705}.There remains a significant medical need for safe and effective new therapies that take into consideration the aging patient population, non-HIV–related comorbidities, virologic resistance, and regimen simplification.

For ART-naive HIV-infected patients, treatment guidelines recommend that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI). Virologically suppressed, HIV-infected patients can benefit by switching from their current regimen to improve safety or tolerability or to simplify the regimen {32519}, {27621}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF) is an oral prodrug of TFV. While TDF is used broadly in the treatment of HIV-1 infection, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs {26885}.

TDF in combination with emtricitabine (FTC) forms a guideline-recommended N(t)RTI backbone for ART-naive HIV-infected patients that can be combined with different third agents. The combination of FTC and TDF is used within several once-daily fixed-dose combinations (FDCs) (Truvada® [FTC/TDF], Atripla® [efavirenz/FTC/TDF], Complera® or Eviplera® [rilpivirine/FTC/TDF], and Stribild® [elvitegravir/cobicistat/FTC/TDF]). Availability of a stand-alone NRTI backbone is important when there is a medical need to use a third agent that is not part of an FDC (eg, ritonavir-boosted PIs), and particularly to provide a range of treatment options in patients with virologic resistance to their third agent but not to the backbone.

Tenofovir alafenamide (TAF) is an investigational oral prodrug of TFV. TAF is more stable in plasma than TDF. It provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF. The distinct metabolism of TAF offers the potential for an improved clinical profile compared with TDF.

Gilead Sciences (Gilead) has coformulated TAF (as TAF fumarate) with FTC into an FDC tablet.

1.2. Emtricitabine/Tenofovir Alafenamide (F/TAF)

F/TAF is a fixed-dose combination (FDC) tablet containing two medications: emtricitabine (FTC) and tenofovir alafenamide (TAF).

The safety of F/TAF FDC is based on two year-long clinical studies (GS-US-292-0104 and GS-US-292-0111) in which 866 treatment-naïve subjects received E/C/F/TAF FDC. The following adverse drug reactions have been identified for F/TAF:

- Very common (more than or equal to 10%): headache, diarrhea, and nausea
- Common (≥ 1% and < 10%): vomiting, abdominal pain, dyspepsia , flatulence, rash, and fatigue

Across all Phase 2 and Phase 3 studies in which 2,394 subjects received E/C/F/TAF FDC, eye disorders were uncommon, balanced between treatment arms, and most were considered by the investigator as unrelated to the study drugs. None were definitive for posterior uveitis, and none resulted in permanent discontinuation of study drugs. One subject in Study GS-US-292-0106 had an adverse reaction of intermediate uveitis (inflammation in the middle of the eye) that was considered related to study drug by the investigator but resolved while the subject continued on study drug without interruption.

For further information on F/TAF, refer to the current version of the investigator's brochure for F/TAF.

1.3. Tenofovir Alafenamide (TAF, GS 7340)

1.3.1. 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 a second generation oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP), a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the elongation of the viral DNA chain. In the development of TAF, three 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.

1.3.2. Preclinical Pharmacology and Toxicology

1.3.2.1. Primary Pharmacodynamics

TAF is metabolized to TFV, a nucleotide analog (i.e., 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 diphosphate (TFV-DP). The cellular enzymes responsible for TFV metabolism to the active diphosphorylated form are adenylate kinase (AK) {13} 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, CD4+ and 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.

1.3.2.2. 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 NOEL for gastrointestinal motility was 100 mg/kg. The IC50 for the inhibitory effect of TAF fumarate (GS-7340-03) on hERG potassium current was estimated to be greater than 10 μM.

1.3.3. Nonclinical Pharmacokinetics

All nonclinical pharmacokinetic 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 pharmacokinetics 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 hrs. 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 CYP3A4 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 UGT1A1 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.

1.3.4. 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 2mg/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 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 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: 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).

1.3.5. Clinical Trials of Single Agent Tenofovir Alafenamide (TAF, GS-7340) or Fixed Dose Combination emtricitabine/tenofovir alafenamide (F/TAF)

A proof-of-concept study, GS-US-120-0104, evaluated monotherapy, with three 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-naïve 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 to 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-PD analysis, a target dose of 20 25 mg TAF monotherapy is expected to provide near maximal activity and ~ 90% reduction in circulating TFV.

The drug interaction potential of F/TAF with other antiretroviral agents was evaluated in GS-US-311-0101 (EFV, DRV/co, COBI), GS-US-120-0117 (RPV), and GS-US-120-0118 (ATV/r, LPV/r, DRV/r, and DTG). The effect of third agents on TAF exposures are summarized in Table 1-1.

Table 1-1. GS-US-311-0101, GS-US-120-0117, and GS-US-120-0118: Changes in TAF exposures when Coadministered with Third Agents

Coadministered Third Agent	TAF AUC (% change)	(90% CI)
EFV	↓14	(↓28 to ↑2)
DRV/co	↓2	(↓20 to ↑19)
COBI	↑165	(↑129 to ↑207)
RPV	↓4	(↓17 to ↑10)
ATV/r	↑91	(↑55 to ↑135)
LPV/r	↑47	(↑17 to ↑85)
DRV/r	↑6	(↓16 to ↑35)
DTG	↑19	(↓4 to ↑48)

In Study GS-US-311-1386, the effect of food (high-calorie, high-fat meal) on the PK of the TAF component of the F/TAF FDC was evaluated. The GLSM ratio of the AUC_{last} of TAF when administered with a high-fat meal was 177% (90% CI: 166% to 188%), and the TAF C_{max} GLSM ratio was 84.5% (90% CI: 74.9% to 95.4%). This ~75% increase in TAF plasma exposure and ~15% decrease in TAF plasma C_{max} when administered with food was accompanied by a delay in T_{max} (increase from 1.00 hour under fasted conditions to 2.00 hours under fed conditions). The exposures of TAF observed under fed or fasted conditions in this study are within the range of exposures observed in the E/C/F/TAF clinical development program and are commensurate with safe and effective plasma levels of TAF (see investigator brochure for further details). Therefore, the changes in TAF exposures when F/TAF is administered with food should not result in differences in efficacy and thus are not clinically relevant. TAF can be administered without regard for food and these findings can be extrapolated to F/TAF (as FTC can be taken without regard to food).

Dose selection considerations for F/TAF that rely on these analyses are outlined in Table 1-2.

Further details for the above clinical studies and other clinical studies of TAF or F/TAF (e.g. TAF in subjects with renal impairment or hepatic impairment) are provided in the F/TAF investigator brochure.

1.3.6. Clinical Trials of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF)

The individual components of F/TAF (ie, FTC and TAF) have been combined with the integrase inhibitor EVG and its pharmacoenhancer cobicistat (COBI, C) in the FDC product E/C/F/TAF, which has been designed to be a complete treatment regimen for HIV-1 infection. The interim data of the 2 clinical studies in ART-naïve patients (GS-US-292-0104 and GS-US-292-0111) and 1 in virologically suppressed patients (GS-US-292-0111) are summarized below.

GS-US-292-0104

This is a randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy and safety of E/C/F/TAF FDC vs STB in HIV-infected, ART-naive adult subjects.

Eligible subjects were ART-naive (excluding pre exposure prophylaxis [PREP] or post exposure prophylaxis [PEP], as admissible, up to 6 months prior to screening), HIV-infected adults with plasma HIV-1 RNA ≥ 1,000 copies/mL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and an eGFR calculated using the Cockcroft Gault method (eGFRCG) ≥ 50 mL/min at screening.

Subjects were randomized in a 1:1 ratio to one of the following 2 treatment groups:

- **Treatment Group 1:** E/C/F/TAF FDC once daily + placebo-to-match STB once daily
- **Treatment Group 2:** STB once daily + placebo-to-match E/C/F/TAF FDC once daily

This summary describes the results of the study through a data cutoff performed when all randomized subjects had completed the Week 48 visit, or had discontinued study treatment before their Week 48 visit:

- The Safety Analysis Set and FAS included 867 (99.4%) subjects (E/C/F/TAF: 435 [99.3%] subjects, STB: 432 [99.5%] subjects).
- For the primary efficacy endpoint analysis (percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm) using the FAS, virologic success rates were as follows: E/C/F/TAF 93.1%, STB 92.4%; difference in percentages (95.002% CI): 1.0% (2.6% to 4.5%). Because the lower bound of the 2-sided 95.002% CI of the difference in the response rate (E/C/F/TAF – STB) was greater than the prespecified 12% noninferiority margin, E/C/F/TAF was determined to be noninferior to STB. Noninferiority was confirmed using the Week 48 PP Analysis Set.
- Overall, the steady state plasma exposure of TAF and TFV, and intracellular exposure of TFV-DP, were in the range of historical data and concurrent study data from the ongoing Phase 3 program. Compared with STB, administration of E/C/F/TAF led to an approximately 90% reduction in mean systemic TFV AUC_{tau} and a higher mean PBMC TFV-DP AUC_{tau}.

- The 48-week AE profile of E/C/F/TAF was generally similar to that of STB with 396 (91.0%) vs 392 (90.7%) subjects reporting any AE, and 36 (8.3%) vs 26 (6.0%) subjects reporting any Grade 3 or 4 AE. The most commonly reported AEs (≥ 10% of subjects in either treatment group) were diarrhea, nausea, upper respiratory tract infection, and headache. There were no clinically relevant differences in AE incidence between treatment groups.

- As noninferiority of E/C/F/TAF to STB was established, multiplicity adjustments were performed for the 4 key safety endpoints at Week 48 in sequential order using a fallback procedure with pre specified 2 sided alpha levels. Based on the adjusted alpha levels, there were statistically significant differences favoring E/C/F/TAF over STB at Week 48 for all 4 safety endpoints: mean percentage changes from baseline in hip BMD ($p < 0.001$) and spine BMD ($p < 0.001$), mean change from baseline in serum creatinine ($p < 0.001$), and incidence of treatment-emergent proteinuria ($p = 0.034$). Other findings of note regarding bone and renal safety included the following:

  — The percentage of subjects with > 3% decrease from baseline to Week 48 in hip or spine BMD was lower in the E/C/F/TAF group than in the STB group (19.0% vs 54.7% for hip and 25.1% vs 45.4% for spine), with statistically significant differences between groups in the categorical distribution of percentage change from baseline to Week 48 in hip or spine BMD ($p < 0.001$).

  — Decreases from baseline in median $eGFR_{CG}$ were smaller in the E/C/F/TAF group than in the STB group ($p < 0.001$), and changes from baseline to Week 48 in $eGFR_{CKD\text{-}EPI,\ creatinine}$ were consistent with those observed in $eGFR_{CG}$.

  — There were no AEs of proximal renal tubulopathy (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy in either treatment group.

- There were no relevant differences in reported eye findings for the study. No eye disorder AEs resulted in discontinuation of study drug. There were no AEs of posterior uveitis during the study.

- Although laboratory abnormalities were common in both treatment groups, the incidence of Grade 3 or 4 abnormalities was balanced between treatment groups. Increases from baseline to Week 48 in total cholesterol, LDL, HDL, total cholesterol to HDL ratio, triglycerides, and serum glucose were larger in the E/C/F/TAF group than in the STB group ($p \leq 0.032$), most likely representing a smaller protective TFV effect with E/C/F/TAF.

GS-US-292-0111

This is a randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy and safety of E/C/F/TAF FDC vs STB in HIV-infected, ART-naive adult subjects. This study has the same study objectives and an identical study design to those of Study GS-US-292-0104, with the following exception:

- While both studies have sites in North America and Europe, Study GS-US-292-0104 includes additional sites in Asia Pacific while Study GS-US-292-0111 includes additional sites in Latin America.

This summary describes the results of the study through a data cutoff performed when all randomized subjects had completed the Week 48 visit, or had discontinued study treatment before their Week 48 visit:

- The Safety Analysis Set and FAS included 866 (99.3%) subjects (E/C/F/TAF: 431 [99.1%] subjects, STB: 435 [99.5%] subjects).

- For the primary efficacy endpoint analysis (percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm) using the FAS, virologic success rates were as follows: E/C/F/TAF 91.6%, STB 88.5%; difference in percentages (95.002% CI): 3.1% (1.0% to 7.1%). Because the lower bound of the 2-sided 95.002% CI of the difference in the response rate (E/C/F/TAF – STB) was greater than the prespecified 12% noninferiority margin, E/C/F/TAF was determined to be noninferior to STB. Noninferiority was confirmed using the Week 48 PP Analysis Set.

- Overall, the 48-week safety profile of E/C/F/TAF was generally similar to that of GS-US-292-0104.

GS-US-292-0109

Study GS-US-292-0109 is a randomized, open-label, multicenter, active-controlled study to evaluate the efficacy, safety, and tolerability of switching to E/C/F/TAF from regimens containing FTC/TDF in virologically suppressed HIV-infected adult subjects. All subjects were drawn from a predefined set of Gilead clinical studies and were virologically suppressed for at least 48 weeks with one of the following FTC/TDF-based regimens:

- STB (Stribild®; EVG/COBI/FTC/TDF)

- ATR (Atripla®; efavirenz (EFV)/FTC/TDF)

- COBI boosted atazanavir (ATV/co)+FTC/TDF (Truvada®; TVD)

- ritonavir boosted atazanavir (ATV/r)+TVD

Subjects enrolled in this study were HIV-infected adults receiving ART regimens for at least 6 consecutive months. All subjects were required to have plasma HIV-1 RNA levels at undetectable levels for at least 6 consecutive months prior to the screening visit; HIV-1 RNA < 50 copies/mL at the screening visit; and an $eGFR_{CG} \geq 50$ mL/min at screening. Subjects must have completed the Week 144 visit in Studies GS-US-236-0102 (US only study), GS-US-236-0103, or GS-US-216-0114; must have completed the Week 96 visit in Study GS-US-264-0110 (subjects taking the EFV-based regimen only); or must have completed the primary endpoint assessment visit in Studies GS-US-236-0104 or GS-US-216-0105.

Subjects were randomized in a 2:1 ratio to one of the following 2 treatment groups:

- **Treatment Group 1:** Switch to E/C/F/TAF FDC once daily
- **Treatment Group 2:** Stay on preexisting FTC/TDF+3rd Agent regimen (STB, ATR, ATV/co+TVD, or ATV/r+TVD)

Randomization was stratified by prior treatment regimen (ie, STB, ATR, ATV/boosted+TVD) at screening.

This data cutoff was performed when all subjects randomized by 31 October 2013 had been followed through the lower limit of Week 48 analysis window (Week 42, or calendar date 28 August 2014) or had discontinued study treatment before this time.

- The Safety Analysis Set included 1436 (99.5%) subjects (E/C/F/TAF: 959 [99.6%] subjects, FTC/TDF+3rd Agent: 477 [99.4%] subjects), and the Week 48 FAS included 1196 (82.9%) subjects (E/C/F/TAF: 799 [83.0%] subjects, FTC/TDF+3rd Agent: 397 [82.7%] subjects).

- For the primary efficacy endpoint analysis (percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm) using the FAS, virologic success rates were as follows: E/C/F/TAF 95.6%, FTC/TDF+3rd Agent 92.9%; difference in percentages (95% CI): 2.7% (-0.3% to 5.6%). Because the lower bound of the 2-sided 95% CI of the difference in the response rate (E/C/F/TAF – FTC/TDF+3rd Agent) was greater than the prespecified 12% noninferiority margin, E/C/F/TAF was determined to be noninferior to FTC/TDF+3rd Agent.

- The incidence and severity of all AEs, and the incidence of SAEs, AEs leading to premature study drug discontinuation, and deaths was similar between treatment groups. The incidence of any study-drug related AE was higher in the E/C/F/TAF group (185 [19.3%] subjects) than in the FTC/TDF+3rd Agent group (61 [12.8%] subjects); however, the incidence of Grade 2, 3, or 4 study drug-related AEs was similar between treatment groups (E/C/F/TAF: 46 [4.8%] subjects, FTC/TDF+3rd Agent: 20 [4.2%] subjects).

- In this study, 4 key secondary safety endpoints were defined and tested in sequential order using a fallback procedure at Week 48. Overall, there were statistically significant differences favoring E/C/F/TAF over FTC/TDF+3rd Agent at Week 48 for all 4 key secondary safety endpoints: mean percentage changes from baseline in hip BMD ($p < 0.001$) and spine BMD ($p < 0.001$), mean change from baseline in serum creatinine ($p < 0.001$), and change from baseline in EFV-related symptom assessment composite score ($p < 0.001$). Other findings of note regarding bone and renal safety included the following:

  — The percentage of subjects with > 3% increase from baseline to Week 48 in hip or spine BMD was greater in the E/C/F/TAF group than in the FTC/TDF+3rd Agent group (25.2% vs 8.6% for hip and 33.6% vs13.8% for spine), with statistically significant differences between treatment groups in the categorical distribution of percentage change from baseline to Week 48 in hip or spine BMD ($p < 0.001$).

— Median (Q1, Q3) changes from baseline to Week 48 in $eGFR_{CG}$ in the E/C/F/TAF and FTC/TDF+3rd Agent groups were 1.8 (-6.6, 9.7) and -3.7 (-11.1, 3.6) mL/min, respectively ($p < 0.001$), and differences between treatment groups in change from baseline to Week 48 in $eGFR_{CKD\text{-}EPI,\ creatinine}$ were consistent with those observed in $eGFR_{CG}$ ($p < 0.001$). The difference between treatment groups in the distribution of proteinuria by urinalysis (dipstick) adjusted for baseline status was statistically significant at Week 48 ($p = 0.004$).

— One subject in the FTC/TDF+3rd Agent group had a nonserious AE of acquired Fanconi syndrome; the event was considered related to the study drug by the investigator and resulted in discontinuation of study drug. Otherwise, there were no AEs of proximal renal tubulopathy (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy in either treatment group.

- There were no relevant differences in eye findings for the study. No eye disorder AEs resulted in discontinuation of study drug. There were no AEs of posterior uveitis during the study. Among subjects who participated in the ophthalmologic substudy (E/C/F/TAF: 32 subjects; FTC/TDF+3rd Agent: 15 subjects), only 1 subject (E/C/F/TAF) with available postbaseline data had a treatment-emergent abnormality, specifically, the detection of a retinal hemorrhage in the left eye. All other subjects had no new abnormalities relative to their baseline fundoscopic examination.

- The incidence of laboratory abnormalities of any grade was balanced between treatment groups for most chemistry, hematology, and urinalysis parameters. Increases from baseline to Week 48 in total cholesterol, LDL, HDL, total cholesterol to HDL ratio, and triglycerides were larger in the E/C/F/TAF group than in the FTC/TDF+3rd Agent group ($p \leq 0.025$), most likely representing a decrease in the protective TFV effect.

Further details for the above clinical studies and other clinical studies of E/C/F/TAF (e.g. E/C/F/TAF in HIV-infected subjects with renal impairment) are provided in the F/TAF investigator brochure.

1.3.7. Clinical Trials of Darunavir/Cobicistat/Emtricitabine/TAF (D/C/F/TAF)

The individual components of F/TAF (ie, FTC and TAF) have been combined with COBI boosted DRV in the FDC product D/C/F/TAF for treatment of HIV-1 infection.

Bioavailability studies demonstrated that when administered as the D/C/F/TAF FDC (TAF 10 mg), TAF exposures were comparable (and corresponding TFV exposures ~ 3 fold higher) to TAF 10-mg exposures, which is consistent with a mixed inhibitory/inductive effect of DRV and COBI on TAF absorption. TAF at 10-mg exposures was deemed appropriate for further evaluation due to the high antiviral activity of TAF at the 8-mg dose, similar to that of TDF-300 mg as monotherapy and given the potency of this regimen.

A randomized, active-controlled Phase 2 Study GS-US-299-0102 compared D/C/F/TAF versus DRV+COBI+FTC/TDF in ART-naive, HIV-infected subjects.

Results from the final analysis demonstrated the following:

- The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL using the Food and Drug Administration (FDA) snapshot algorithm was similar between treatment groups at Week 24 (primary efficacy endpoint) (74.8% in the D/C/F/TAF group and 74.0% in the DRV+COBI+TVD group), but numerically lower in the D/C/F/TAF group at Week 48 (76.7% in the D/C/F/TAF group and 84.0% in the DRV+COBI+TVD group).

- At Week 48, the difference in rates of virologic success between treatment groups was primarily due to a difference in the numbers of subjects who discontinued study drug due to other reasons and had the last available HIV-1 RNA ≥ 50 copies/mL (D/C/F/TAF: 8.7%; DRV+COBI+TVD: 4.0%) or < 50 copies/mL (D/C/F/TAF: 6.8%; DRV+COBI+TVD: 2.0%).

- Importantly, D/C/F/TAF demonstrated a potential benefit over DRV+COBI+FTC/TDF in terms of renal and bone safety: smaller median decreases in $eGFR_{CG}$ (mL/min) (at Week 48, D/C/F/TAF -2.9 vs DRV+COBI+FTC/TDF -10.6 [p = 0.017]) and smaller mean percentage decreases in BMD (at Week 48, spine D/C/F/TAF -1.57% vs DRV+COBI+FTC/TDF -3.62% [p = 0.003], hip -0.84% vs -3.82% [p < 0.001]). These mean percentage changes from baseline to Week 48 in spine and hip BMD with D/C/F/TAF are both lower than all published studies of Week 48 BMD data in ART-naive subjects receiving an NRTI-containing ART regimen {25124}, {25126}, {16658}, {21057}.

- Treatment with D/C/F/TAF or DRV+COBI+TVD was generally well tolerated during this study. No unexpected AEs were associated with the use of D/C/F/TAF through 48 weeks of treatment. Most treatment-emergent AEs were assessed as Grade 1 or Grade 2 in severity. The incidence of Grade 3 AEs was comparable between the 2 groups (D/C/F/TAF 6.8%, DRV+COBI+TVD 8.0%). No Grade 4 AEs were reported during the study. Similar percentages of subjects in each treatment group had SAEs (D/C/F/TAF 4.9% vs. DRV+COBI+TVD 4.0%), most of which were unrelated to study drug.

1.4. Emtricitabine (FTC, Emtriva®)

Further information regarding Emtriva® is available in the current investigator's brochure and local label; an overview is provided below.

1.4.1. 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 QD dose concurrently with other ARVdrugs. The 200 mg FTC capsule formulation was approved by the US Food and Drug Administration (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 antiretroviral drugs in both adult and

pediatric patients. In pediatric patients, the recommended dose of Emtriva® is 6 mg/kg QD, up to a maximum of 200 mg QD 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.

1.5. Information about Fixed Dose Combination of Abacavir/Lamivudine (ABC/3TC, Epzicom®, Kivexa®)

Epzicom® or Kivexa® is the brand name for the fixed dose combination of abacavir 300 mg/lamivudine 600 mg (ABC/3TC). Epzicom® or Kivexa® is recommended for use once daily in adults.

Please refer to the latest version of the SmPC and/or Prescribing Information for Epzicom® or Kivexa® for additional information.

1.6. Rationale for This Study

Gilead is developing the fixed-dose combination (FDC) product emtricitabine/tenofovir alafenamide (F/TAF) for the treatment of HIV-1 infection in combination with other antiretroviral agents. TAF, one component of F/TAF is an improved prodrug for tenofovir, and for clinicians, F/TAF can provide flexibility in constructing an effective antiretroviral regimen for patients.

The Phase 1 study (GS-US-120-0104) demonstrated that TAF has an improved pharmacokinetic profile relative to TDF (longer plasma half-life, lower plasma TFV exposure, and higher intracellular TFV-DP exposure) with greater antiviral activity at 25 mg dose.

As a nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) backbone, F/TAF is being evaluated as part of E/C/F/TAF FDC (150/150/200/10 mg) in several Phase 3 studies across broad patient populations. The interim data from these studies demonstrated potent efficacy of E/C/F/TAF with improved renal and bone safety profile relative to STB in ART-naive patients (GS-US-292-0104 and GS-US-292-0111) and to TDF-containing regimens (including E/C/F/TDF) in virologically suppressed patients (GS-US-292-0109). In addition, the efficacy and safety of F/TAF FDC (200/10 and 200/25 mg) is being evaluated in Study GS-US-311-1089, an ongoing, Phase 3, randomized, double-blind study in HIV-infected subjects who are virologically suppressed on regimens containing FTC/TDF.

As ABC/3TC is another N[t]RTIs backbone for the treatment of HIV-1 infection in combination with other antiretroviral agents, it is of interest to conduct a randomized controlled study in patients who are virologically suppressed on a ABC/3TC containing regimen that compares efficacy and safety between patients who switch to F/TAF vs. those who maintain ABC/3TC while continuing the same third agent.

1.7. Rationale for Dose Selection

The 200 mg dose of FTC represents the marketed dose for this agent that is currently available as single agent capsules (Emtriva®) and as a component of a number of fixed-dose combination tablets, including: Truvada®, Atripla®, Complera®/Eviplera®, and Stribild®.

The recommended dose of F/TAF (200/10 mg or 200/25 mg) per third ARV agent is based on ensuring that patients have a TAF systemic exposure that is comparable to the TAF 25 mg exposure, the common reference exposure for which an extensive E/C/F/TAF safety and efficacy database exists.

The different TAF dose (10 or 25 mg) is generally based on whether or not the coadministered third agent has any clinically relevant effect on TAF (eg, via inhibition of intestinal Pgp, termed as "boosting" for simplicity).

Specifically, F/TAF (200/10 mg) will be used with third agents that substantially increase TAF exposure (ATV/r, LPV/r), and F/TAF (200/25 mg) will be used with third agents that do not have clinically relevant effect on TAF exposure (EFV, RPV, DTG). Although DRV/r did not demonstrate any clinically relevant "boosting" effect on TAF, clinical data from a Phase 2, randomized, double-blind, active-controlled study evaluating efficacy and safety of a regimen containing D/C/F/TAF compared with DRV+COBI+FTC/TDF in HIV-1 infected, ART-naïve subjects provides support for using F/TAF 200/10 mg with DRV/r. In that study, D/C/F/TAF was noninferior to DRV+COBI+TVD when administered for 24 weeks using the FDA snapshot algorithm with HIV-1 RNA cutoff at 50 copies/mL, in accordance with the primary objective of this study.

Based on these considerations, the proposed dose of F/TAF FDC tablets per third ARV agent is listed in Table 1-2, which presents the TAF-equivalent dose achieved based on systemic TAF exposure resulting from administration of the recommended F/TAF dose with each coadministered third ARV agent.

Table 1-2. Dose Recommendations for F/TAF with Potential Concomitant Antiretroviral Drugs

ARV Drug	Recommended F/TAF Dose (mg)	TAF-Equivalent Dose[a] (mg)
EFV	200/25	12[b]
RPV		24
DTG[c]		17[b]/30
RAL		—[d]
MVC		—[d]
NVP		—[d]
ATV+COBI	200/10	—[e]
ATV+RTV		19
DRV+COBI		11
DRV+RTV		11
LPV/r		15

TAF-Equivalent Dose calculated based on percentage change in TAF AUC with/without coadministered drug.
a Expected exposure in fed state unless otherwise noted.
b Expected exposure in fasted state.
c Because DTG may be administered without regard to food, expected exposures are provided for both the fed and fasted states.
d No DDI study performed. Dosing recommendation based on the nonclinical profiles of TAF and the specified ARV.
e No DDI study performed. Dosing recommendation extrapolated based on nonclinical information and the DDI study between TAF and ATV+RTV.

While no clinical drug-drug interaction studies of TAF were conducted with raltegravir (RAL), MVC and NVP, no clinically relevant drug-drug interaction is expected based upon nonclinical and clinical information.

Taken together, F/TAF (200/10 or 200/25 mg) in combination with the appropriate third agent can achieve plasma TAF exposure that is associated with potent antiviral activity and with lower plasma TFV exposure than that seen with TDF 300 mg.

The complete list of allowed third agents and the corresponding F/TAF dose are presented in Table 3-1.

Lastly, the food effect on TAF was evaluated when administered as part of E/C/F/TAF FDC (GS-US-292-0110) and as F/TAF FDC (GS-US-311-1386). Under fed conditions (high fat meal), TAF exposures increased by 17% with E/C/F/TAF FDC and 77% with F/TAF FDC However, these TAF exposures observed under fed or fasted conditions in this study are within the range of exposures observed in the E/C/F/TAF FDC clinical development program and are commensurate with safe and effective TAF exposure. Therefore, these data support the administration of F/TAF without regard to food.

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 evaluate the efficacy of switching ABC/3TC to F/TAF versus maintaining ABC/3TC in HIV-1 infected subjects who are virologically suppressed on regimens containing ABC/3TC as determined by the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48

The secondary objectives of this study are:

- To evaluate the efficacy, safety and tolerability of two regimens through Week 48 and Week 96

- To evaluate the bone safety of two regimens as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Week 48 and Week 96

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot algorithm

The secondary endpoints of this study are:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 96 as defined by the FDA snapshot algorithm

- The percent change from baseline in hip and spine BMD at Week 48 and Week 96

3.2. Study Design

This protocol describes a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of switching ABC/3TC to F/TAF fixed-dose combination (FDC) tablet versus continuing ABC/3TC in HIV-1 infected subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen containing ABC/3TC for ≥ 6 consecutive months prior to screening.

All subjects will be randomized, in a blinded fashion, in a 1:1 ratio to either switch from ABC/3TC to F/TAF + placebo-to-match ABC/3TC or maintain the ABC/3TC + placebo-to-match F/TAF while continuing the protocol allowed third agent (as prescribed by the Investigator) in their antiretroviral (ARV) regimen.

3.3. Study Treatments

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

Treatment Arm 1: F/TAF + Placebo-to-match ABC/3TC; third antiretroviral agent remains the same (n = 250)

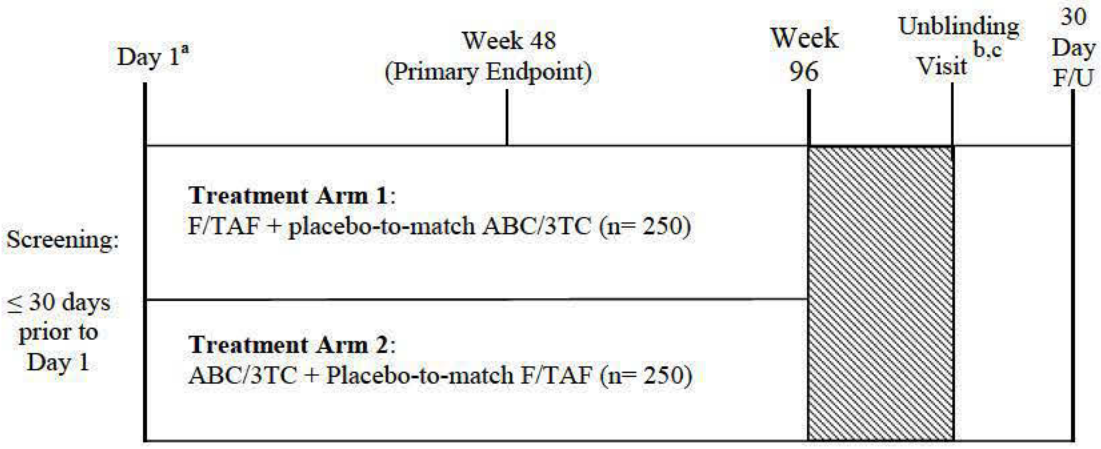
Treatment Arm 2: ABC/3TC + Placebo-to-match F/TAF; third antiretroviral agent remains the same (n = 250)

Since different antiretroviral third agents require different doses of TAF, randomization will be stratified by the third agents: boosted protease inhibitors vs. other agents.

Table 3-1. Recommended F/TAF dose by co-administered third agent:

Treatment Arm 1	Allowed Third Agents
F/TAF (200/10 mg)	LPV/r, ATV+RTV, ATV+COBI (or ATV/COBI FDC), DRV+RTV, DRV+COBI (or DRV/COBI FDC)
F/TAF (200/25 mg)	EFV, RPV, RAL, DTG, MVC, NVP

Figure 3-1. Study Schema



a Following the Day 1 visit, subjects will return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Week 96.
b After Unblinding visit, in countries where F/TAF FDC is not commercially available, subjects (except in certain countries such as UK) will be given the option to receive the open-label F/TAF FDC and attend study visits every 12 weeks until it becomes commercially available, or until Gilead Sciences terminates the study in that country. Subjects who complete the study through Unblinding and do not wish to continue to participate (including all subjects in certain countries such as UK) will be required to return to the clinic 30 days after the completion of the study drug for a 30-Day follow-up visit.
c Subjects who have discontinued study drug before Week 96 will not be eligible for the extension phase of the study; these subjects will be asked to continue attending the scheduled study visits through Unblinding.

3.4. Duration of Treatment

The treatment duration is 96 weeks. After screening, eligible subjects will be randomized to Treatment Arm 1 or 2 and treated for 96 weeks. Following the Screening and Day 1 visits, subjects will return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Week 96.

Subjects will be treated for 96 weeks in the randomized phase. After Week 96, subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments have been unblinded. After unblinding, in countries where F/TAF FDC is not commercially available, subjects (except in certain countries such as UK) will be given the option to receive the open-label F/TAF FDC and attend study visits every 12 weeks until it becomes commercially available, or until Gilead Sciences terminates the study in that country.

Subjects who complete the study through Unblinding Visit and do not wish to receive open-label F/TAF FDC will be required to return to the clinic for a 30-Day Follow Up visit.

After the Unblinding Visit, subjects in certain countries (eg UK) per requirement must stop taking study drug and complete a 30-Day Follow Up visit.

3.5. Biomarker Testing

3.5.1. Samples for Optional Future Research

In addition to the study-specific informed consent to be signed by each subject participating in the study, a separate, specific signature will be required to document a subject's agreement to provide additional samples or to allow the use of the remainder of their already collected PK specimens for optional future research, once approved by local authorities as applicable according to specific local regulations.

The specimens collected for optional future research will be used to increase our knowledge and understanding of the biology of the study disease and related diseases and to study the association of biomarkers with disease pathogenesis, progression and/or treatment outcomes, including efficacy, adverse events, and the processes of drug absorption and disposition. These specimens may be used also to develop biomarker or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional future research specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 500 subjects who meet the eligibility criteria will be enrolled.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1. The ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures

2. Age ≥ 18 years

3. Currently receiving antiretroviral regimen containing ABC/3TC FDC in combination with one third agent for ≥ 6 consecutive months prior to Screening. Refer to Table 4-1 for allowed third agents of the pre-existing regimen; ABC/3TC/DTG (Triumeq® FDC) is not an allowed pre-existing regimen

4. Plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 months preceding the screening visit (measured at least twice using the same assay) and not experienced two consecutive HIV-1 RNA above detectable levels after achieving a confirmed (two consecutive) HIV-1 RNA below detectable levels on the current regimen in the past year

   To determine virologic suppression in the preceding 6 months prior to screening, the lower limit of quantification (LLOQ) by the local HIV-1 RNA assay may be used, only if its LLOQ is greater than 50 copies/mL (e.g. LLOQ of 75 copies/mL)

5. Plasma HIV-1 RNA levels < 50 copies/mL at Screening Visit

6. Normal ECG (or if abnormal, determined by the Investigator to be not clinically significant)

7. Estimated GFR ≥ 50 mL/min according to the Cockcroft Gault formula for creatinine clearance {2202}:

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

   Female: $\frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})} = \text{CLcr (mL/min)}$

8. Hepatic transaminases (AST and ALT) ≤ 5 × upper limit of normal (ULN)

9. Total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin (subjects with documented Gilbert's syndrome or with atazanavir-associated hyperbilirubinemia may have total bilirubin up to 5 x ULN)

10. Adequate hematologic function (absolute neutrophil count ≥ 1,000/mm^3; platelets ≥ 50,000/mm^3; hemoglobin ≥ 8.5 g/dL)

11. Serum amylase ≤ 5 × ULN (subjects with serum amylase > 5 × ULN will remain eligible if serum lipase is ≤ 5 × ULN)

12. A female subject is eligible to enter the study if it is confirmed that she is:

    a. Not pregnant or nursing
    b. Of non-childbearing potential (e.g., women who have had a hysterectomy, have had both ovaries removed or medically documented ovarian failure, or are postmenopausal women > 54 years of age with cessation (for ≥12 months) of previously occurring menses).
    c. Of childbearing potential (as defined in Appendix 5) and agrees to utilize highly effective contraception methods or be non-heterosexually active or practice sexual abstinence (as defined in Appendix 5) from screening throughout the duration of study treatment and for 30 days following discontinuation of study drugs.
    d. Female subjects who utilize hormonal contraceptive as one of their birth control methods must have used the same method for at least three months prior to study dosing.

13. Male subjects must agree to utilize a highly effective method of contraception (as defined in Appendix 5) during heterosexual intercourse or be non-heterosexually active, or practice sexual abstinence from first dose throughout the study period and for 30 days following the last study drug dose.

    a. Male subjects must agree to refrain from sperm donation from first dose until at least 30 days after the last study drug dose.

Table 4-1. Allowable Antiretroviral Agents of Pre-Existing Regimen

Antiretroviral Class	Agents
Boosted PI	LPV/r, ATV+RTV, ATV+COBI (or ATV/COBI FDC), DRV+RTV, DRV+COBI (or DRV/COBI FDC)
NNRTI	EFV[a], RPV[a], NVP
INSTI	RAL, DTG[a]
CCR5 inhibitor	MVC

a DTG is allowed only when administered as an individual agent, but not as part of single tablet regimen (i.e. ABC/3TC/DTG)
b Change of pharmacoenhancer between RTV and COBI in itself, including change from PI+RTV to PI/COBI, is not considered as change of regimen

4.3. Exclusion Criteria

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

1. A new AIDS-defining condition diagnosed within the 30 days prior to screening (except CD4 cell count and/or percentage criteria) (refer to Appendix 6)

2. Hepatitis B surface antigen (HBsAg) positive

3. Subjects experiencing decompensated cirrhosis (e.g., ascites, encephalopathy, etc.)

4. Subjects receiving ongoing treatment with bisphosphonate to treat bone disease (e.g. osteoporosis)

5. Females who are breastfeeding

6. Positive serum pregnancy test

7. Have an implanted defibrillator or pacemaker

8. Current alcohol or substance use judged by the Investigator to potentially interfere with subject study compliance

9. A history of malignancy within the past 5 years (prior to screening) or ongoing malignancy other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Subjects with cutaneous KS are eligible, but must not have received any systemic therapy for KS within 30 days of Day 1 Visit and must not be anticipated to require systemic therapy during the study

10. Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to Day 1 Visit

11. Any other clinical condition or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements

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

13. Medications excluded due to the potential for interaction with FTC, TAF, ABC or 3TC (Table 5-2). Administration of any Prohibited Medication (Table 5-2) must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study. Use of Medications to Be Used With Caution (Table 5-2) are allowed and are at the discretion of the Principal Investigator.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

Subjects will be assigned a screening number at the time of consent.

Randomization and Day 1 visit cannot occur until subject eligibility has been confirmed.

Once eligibility has been confirmed, each subject will be assigned a unique subject number using Interactive Web Response System (IWRS). Once a subject number has been assigned to a subject, it will not be reassigned to any other subject. The subject number assignment and randomization may be performed up to 7 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed.

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

Randomization will be stratified by the third agents (boosted protease inhibitors vs. any other protocol allowed third agents) in a subject's existing regimen.

Treatment Arm 1: F/TAF + Placebo-to-match ABC/3TC; the third ARV agent (as prescribed by the Investigator) of the subjects' regimen should remain the same during the subjects' participation in the study (n = 250)

Treatment Arm 2: ABC/3TC + Placebo-to-match F/TAF; the third ARV agent (as prescribed by the Investigator) of the subjects' regimen should remain the same during the subjects' participation in the study (n = 250)

IWRS will assign blinded study drug bottle numbers at each study visit until the Unblinding Visit. Study drug will be dispensed to the subject in a blinded fashion. **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.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IWRS system for that subject. Gilead 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 subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), 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 treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Drug Safety and Public Health (DSPH) 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) Tablets and matching placebo

For subjects randomized to Treatment Arm 1, F/TAF and placebo-to-match F/TAF tablets will be provided by the Sponsor. Emtricitabine /Tenofovir Alafenamide 200/25 mg tablets are rectangular-shaped, film-coated blue tablets and are debossed with "GSI" on one side of the tablet and "225" on the other side of the tablet. The F/TAF tablet cores contain 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 Blue #2/indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Emtricitabine /Tenofovir Alafenamide 200/10 mg tablets are rectangular-shaped, film-coated gray tablets and are debossed with "GSI" on one side of the tablet and "210" on the other side of the tablet. The F/TAF tablet cores contain 200 mg of emtricitabine and 10 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 iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Placebo-to-match F/TAF 200/25 mg tablets are rectangular-shaped, film-coated blue tablets and are debossed with "GSI" on one side of the tablet and "225" on the other side of the tablet. 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.

Placebo-to-match F/TAF 200/10 mg tablets are rectangular-shaped, film-coated gray tablets and are debossed with "GSI" on one side of the tablet and "210" on the other side of the tablet. Placebo tablets contain croscarmellose sodium, magnesium stearate, lactose and microcrystalline cellulose. The tablet cores are film-coated with iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

5.2.1.2. Abacavir/Lamivudine (ABC/3TC) and matching placebo

Abacavir/Lamivudine (ABC/3TC) tablets are commercially sourced. Information regarding the formulation of commercially available Abacavir/Lamivudine (ABC/3TC) can be found in the current prescribing information.

Placebo-to-match Abacavir/Lamivudine (ABC/3TC) tablets are capsule-shaped, film-coated orange tablets and are debossed with "GS FC2" on one side of the tablet and plain faced on the other side of the tablet. Placebo tablets are identical in appearance to the active tablets. Placebo tablets contain croscarmellose sodium, magnesium stearate, lactose and microcrystalline cellulose. The tablet cores are film-coated with Yellow #6/sunset yellow FCF aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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.

Abacavir/Lamivudine (ABC/3TC) tablets and placebo-to-match ABC/3TC tablets are packaged in a white high density polyethylene (HDPE) bottle. Each bottle contains 30 tablets. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed and aluminum-faced liner.To ensure stability of the tablets and proper product identification, the drug should not be stored in a container other than the container in which it is supplied.

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 Food and Drug Administration (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 and the placebo-to-match Emtricitabine/Tenofovir Alafenamide 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.

Abacavir/Lamivudine (ABC/3TC) and the placebo-to-match Abacavir/Lamivudine (ABC/3TC) 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 subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability of the tablets and proper product identification, the drug product should not be stored in a container other than the container in which it is supplied. Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

The third ARV agent of the subjects' pre-existing regimen should be stored according to the approved product labeling for each particular component.

5.3. Dosage and Administration

F/TAF, placebo-to-match F/TAF, ABC/3TC and placebo-to-match ABC/3TC fixed-dose combination tablets will be provided by Gilead Sciences. The third antiretroviral agent of the subjects' pre-existing regimen will be prescribed by the Investigator, and the subject is responsible for obtaining the third ARV agent prior to Day 1 visit. As both F/TAF and ABC/3TC can be taken without regard to food, subjects should be instructed to comply with the food or fasting requirements of the third agent, if any.

Treatment Arm 1: F/TAF FDC tablet (200/10 mg or 200/25 mg) + placebo-to-match ABC/3TC FDC tablet in combination with a third antiretroviral agent administered orally once daily (QD) (at approximately the same time every day) with the recommended dose by co-administered third agent as summarized below.

Table 5-1. Recommended F/TAF Dose by Co-administered Third Agent

Treatment Arm 1	Allowed Third Agents
F/TAF (200/10 mg)	LPV/r, ATV+RTV, ATV+COBI (or ATV/COBI FDC), DRV+RTV, DRV+COBI (or DRV/COBI FDC)
F/TAF (200/25 mg)	EFV, RPV, RAL, DTG, MVC, NVP

Treatment Arm 2: Current antiretroviral drug regimen containing ABC/3TC + placebo-to-match F/TAF FDC tablet in combination with a third antiretroviral agent administered orally, QD (at approximately the same time each day)

Subjects will be instructed to bring all study medication in the original container at each clinic visit for drug accountability (unless otherwise specified in the study procedures sections of this protocol).

Antiretroviral agents that are not specified in Table 5-1 will be prohibited.

5.4. Prior and Concomitant Medications

The use of medications for the treatment of HIV, other than the study treatment (i.e. F/TAF or ABC/3TC) and baseline third agent is prohibited. Medications listed in the following table and use of herbal/natural supplements are excluded or should be used with caution while subjects are participating in the study due to potential drug-drug interactions with the study drugs.

Table 5-2. Prior and Concomitant Medications

Medications to be avoided and medications to be used with caution due to the potential for drug-drug interaction with FTC, TAF, ABC or 3TC are as follows:

Medication Class	Prohibited Medications	Medications to be used with caution
Antiarrhythmics		amiodarone, quinidine: May increase concentration of TAF and/or TFV
Antibacterials		Trimethoprim/Sulfamethoxazole (160/800 mg): TMP/SMX increases the exposure of lamivudine.
Anticonvulsants	carbamazepine, oxcarbazepine, phenobarbital, phenytoin	
Antifungals		itraconazole, ketoconazole, voriconazole: may increase concentration of TAF and/or TFV
Antimycobacterials	rifabutin, rifampin, rifapentine	clarithromycin: may increase concentration of TAF and/or TFV
Bisphosphonate	Any agent in this class (for example: alendronate, ibandronate, risedronate, zoledronate, pamidronate, teriparatide)	
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.
Ethanol		Ethanol: Ethanol decreases the elimination of abacavir causing an increase in overall ABC exposure
Herbal/Natural Supplements	St. John's wort (Hypericum perforatum), Echinacea, Milk thistle (i.e. silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	

Medication Class	Prohibited Medications	Medications to be used with caution
Methadone		Methadone: Coadministration of ABC with methadone increases oral methadone clearance This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.
Other	probenecid	

Should subjects have a need to initiate treatment with any excluded concomitant medication, the Gilead Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator must notify Gilead Sciences as soon as he/she is aware of the use of the excluded medication.

Additionally, Investigators should refer to the product/package inserts of the other antiretroviral medications for contraindications related to their use.

5.5. Changes in Antiretroviral Therapy

Prior to the Unblinding Visit and during the open-label extension phase of the study, subjects and Investigators are not permitted from changing the third agent.

5.6. Dispensing and Accountability of Investigational Medicinal Product (IMP)

The Investigator is responsible for ensuring adequate accountability of all used and unused IMP. The Investigator [or designee (e.g., study center pharmacist)] will acknowledge receipt of the study drugs from Gilead Sciences (or designee) after reviewing the shipment's content and condition. The Investigator (or designee) will be responsible for maintaining an accurate inventory (on IMP accountability records) of the dates and quantities of all study drugs received, dispensed, and returned. Each dose of the study drug administered at the study center will be administered by qualified study center personnel. All doses of study drug administered to subjects in the clinic under the supervision of staff will be accurately recorded on the Investigational Product Inventory Logs provided by Gilead Sciences (or on equivalent documentation maintained by the study center), which indicates the date and quantity of all doses of study drug(s) dispensed to individual subjects. 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 IMP inventory and dispensing logs must be available for inspection by the study monitor. Study medication supplies, including partially used or empty bottles, must be accounted for by the study monitor prior to destruction or return.

IMP accountability records will be provided to each study site to:

- Record the date received and quantity of IMP kits
- Record the date, subject number, subject initials, the IMP kit number dispensed
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

5.7. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP 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 IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

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

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

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

Any deviation from protocol procedures should be noted in the subject's clinical chart and appropriate eCRFs. In addition, the Sponsor or Contract Research Organization (CRO) should be promptly notified of any protocol deviations.

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible for study prior to enrollment. Please refer to Section 5 for details about randomization and treatment assignment.

6.2. Pretreatment Visit Assessments

6.2.1. Screening Visit

Subjects will be screened within 30 days before Day 1 visit to determine eligibility for participation in the study. The following will be performed and documented at screening:

6.2.1.1. Obtain written informed consent

6.2.1.2. Obtain medical history including history of HIV-1 disease-related events and prior medications within 30 days of the Screening visit

6.2.1.3. Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)

6.2.1.4. Vital signs (blood pressure, pulse, respiration rate, and temperature), body weight, and height

6.2.1.5. 12-lead ECG performed supine

6.2.1.6. Urine collection for the following laboratory procedures:

6.2.1.6.1. Urinalysis and urine chemistry

6.2.1.7. Blood sample collection for the following laboratory analyses:

6.2.1.7.1. Serum pregnancy test (females of childbearing potential only). If the test is positive, the subject will not be enrolled.

6.2.1.7.2. Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase $> 1.5 \times$ ULN)

6.2.1.7.3. Estimated GFR according to the Cockcroft Gault formula for creatinine clearance:

i. Male: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = \text{CLcr (mL/min)}$

ii. Female: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} \times 0.85 = \text{CLcr (mL/min)}$

6.2.1.7.4. Hematology profile: complete blood count (CBC) with differential and platelet count

6.2.1.7.5. CD4+ cell count

6.2.1.7.6. Plasma HIV-1 RNA

6.2.1.7.7. Hepatitis B surface antigen (HBsAg) serology

6.2.1.8. Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days after screening for the Day 1 assessments.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events 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.

6.2.2. Day 1 Visit

The following evaluations are to be completed at the Day 1 Visit. The subject must complete all Day 1 assessments before being dispensed the study drug. Initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit.

6.2.2.1. DXA Scan (spine and hip)

6.2.2.1.1. The DXA scan will be performed on subjects once eligibility is confirmed and prior to study drug administration at the Day 1 Visit. The scan may be performed prior to or on the Day 1 Visit so long as it occurs before dosing

6.2.2.2. Review of AEs and changes in concomitant medications

6.2.2.3. Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)

6.2.2.4. Vital signs (blood pressure, pulse, respiration rate, and temperature), including weight

6.2.2.5. Urine collection for the following laboratory procedures:

6.2.2.5.1. Urinalysis and urine chemistry

6.2.2.5.2. Evaluations of renal tubular function (collected fasted): If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a urine sample for these evaluations.

6.2.2.5.3. Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive at Day 1 visit, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will not be able to participate.

6.2.2.5.4. Urine sample storage for possible additional clinical testing

6.2.2.6. Blood sample collection for the following laboratory analyses:

6.2.2.6.1. Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase $> 1.5 \times$ ULN)

6.2.2.6.2. Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

6.2.2.6.3. Estimated GFR, according to the Cockcroft Gault formula for creatinine clearance

6.2.2.6.4. Hematology profile: CBC with differential and platelet count

6.2.2.6.5. Plasma HIV-1 RNA

6.2.2.6.6. CD4+ cell count

6.2.2.6.7. Hepatitis C virus antibody (HCVAb) serology. If the antibody test result is positive, HCV RNA test will be performed to confirm HCV viremia

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

6.2.2.6.9. Serum sample storage for possible additional clinical testing (for subjects who provide consent)

6.2.2.6.10. Evaluations of bone turnover (collected fasted): If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for these evaluations

6.2.2.6.11. Evaluations of inflammation, including but not limited to cystatin-C, IL 6, hs CRP, d-dimer, sCD14, and sCD163

6.2.2.6.12. Evaluations of platelet function, including but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand

6.2.2.6.13. Platelet function for substudy subjects (only at selected sites)

6.2.2.6.14. Whole blood sample storage for virology analyses

6.2.2.7. Obtain subject number and randomize the subject via the IWRS. The subject number assignment may be performed up to 7 days prior to the in clinic Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed

6.2.2.8. Study drug dispensation: Investigators must provide a prescription to the subjects for the third ARV agent in their pre-existing regimen. The subject is responsible for obtaining the third ARV prior to or during the study visit

6.2.2.8.1. Study drug will be dispensed in a blinded fashion

6.2.2.8.2. All subjects will take 2 tablets daily, in addition to the third ARV agent

6.2.2.8.3. Subjects must initiate dosing of study drug within 24 hours after the Day 1 visit

6.2.2.9. Subjects should also be counseled regarding the importance of adherence and taking their study medications in the morning at approximately the same time each day

For subjects in Germany, DXA scans will not be performed at any study visit.

6.3. Treatment Assessments

6.3.1. Treatment Visits (Weeks 4 – 48)

The following evaluations are to be completed at the end of Weeks 4, 8, 12, 24, 36 and 48 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 completed within ± 6 days of the protocol-specified visit date through Week 36, unless otherwise specified. The visit window at Week 48 will be ± 6 weeks of the protocol-specified visit date, and this clinical visit window coincides with the Week 48 statistical analysis window for HIV RNA.

Regularly scheduled evaluations will be made on all subjects whether or not they continue to receive study drug.

6.3.2.1. DXA Scans (spine and hip) (**Weeks 24 and 48;** can be performed **≤ 10 days** before study visit)

6.3.2.2. Review of AEs and changes in concomitant medications

6.3.2.3. Complete physical examination (**Weeks 24 and 48**) (urogenital/anorectal exams will be performed at the discretion of the Investigator)

6.3.2.4. Symptom-directed physical examination as needed (**Weeks 4, 8, 12, 36**)

6.3.2.5. 12-lead ECG performed supine **(Week 48 only)**

6.3.2.6. Vital signs (blood pressure, pulse, respiration rate, and temperature), including weight

6.3.2.7. Urine collection for the following laboratory procedures:

6.3.2.7.1. Urinalysis and urine chemistry

6.3.2.7.2. Evaluations of renal tubular function (collected fasted): If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a urine sample for these evaluations. (**Weeks 4, 12, 24 and 48**)

6.3.2.7.3. Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be discontinued.

6.3.2.7.4. Urine sample storage for possible additional clinical testing

6.3.2.8. Blood sample collection for the following laboratory analyses:

6.3.2.8.1. Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). **At Weeks 24 and 48, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.**

6.3.2.8.2. Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments (**Weeks 24 and 48 only**)

6.3.2.8.3. Estimated GFR, according to the Cockcroft Gault formula for creatinine clearance

6.3.2.8.4. Hematology profile: CBC with differential and platelet count

6.3.2.8.5. Plasma HIV-1 RNA

6.3.2.8.6. CD4+ cell count

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

6.3.2.8.8. Serum sample storage for possible additional clinical testing (for subjects who provide consent)

6.3.2.8.9. Evaluations of bone turnover (collected fasted): If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for these evaluations. (**Weeks 4, 12, 24 and 48**)

6.3.2.8.10. Evaluations of inflammation, including but not limited to cystatin-C, IL 6, hs CRP, d-dimer, sCD14, and sCD163 (**Weeks 4, 12, 24 and 48**)

6.3.2.8.11. Evaluations of platelet function, including but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand (**Weeks 4, 12, 24 and 48**)

6.3.2.8.12 Platelet function for substudy subjects (only at selected sites) **(Weeks 4 and 12)**

6.3.2.8.13 Single whole blood sample collection (**Week 4 only**): PBMC sample processing will be performed by the central laboratory; TFV-DP concentrations in PBMCs will be determined.

6.3.2.9. Pharmacokinetic Blood Collection:

6.3.2.9.1. A single PK blood sample should be collected as part of the safety laboratory blood draws at any time pre-or post-dose (**Weeks 8, 12, 24 and 36**)

6.3.2.9.2. A single PK blood sample will be collected after an observed in-clinic dose 15 minutes to 4 hours post dose (**Weeks 4 and 48 only**).

- Subjects may take their previous day's dose at their regular dosing time.
- Subjects should be reminded not to take their dose of study medication prior to their clinic visit; instead, subjects should bring their dose of study medication to the clinic
- If the subject has taken their dose of study drugs prior to the visit, the visit may proceed, but the subject must return with 72 hours in a fasted state for the observed dose and post-dose PK collection

6.3.2.10. Subjects who meet the criteria for virologic rebound should be managed according to Management of Virologic Failure (Section 6.9)

6.3.2.11. Document study drug dispensation and accountability for all study drugs dispensed

6.3.2. Treatment Visits (Weeks 60-96)

The following evaluations are to be completed at the end of Weeks 60, 72, 84, and 96 unless otherwise specified.

Study visits are to be completed within ± 6 days of the protocol-specified visit date through Week 84 unless otherwise specified. The visit window at Week 96 will be ± 6 weeks of the protocol-specified visit date, and this clinical visit window coincides with the Week 96 statistical analysis window for HIV RNA.

Regularly scheduled evaluations will be made on all subjects whether or not they continue to receive study drug.

6.3.3.1. DXA Scans (spine and hip) (**Weeks 72 and 96;** can be performed **≤ 10 days** before study visit)

6.3.3.2. Review of AEs and changes in concomitant medications

6.3.3.3. Complete physical examination (**Weeks 72 and 96**) (urogenital/anorectal exams will be performed at the discretion of the Investigator)

6.3.3.4. Symptom-directed physical examination as needed (**Weeks 60 and 84**)

6.3.3.5. 12 lead ECG performed supine (**Week 96**)

6.3.3.6. Vital signs (blood pressure, pulse, respiration rate, and temperature), including weight

6.3.3.7. Urine collection for the following laboratory procedures:

6.3.3.7.1. Urinalysis and urine chemistry

6.3.3.7.2. Evaluations of renal tubular function (collected fasted): If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a urine sample for these evaluations. (**Week 72 and 96**)

6.3.3.7.3. Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be discontinued.

6.3.3.7.4. Urine sample storage for possible additional clinical testing

6.3.3.8. Blood sample collection for the following laboratory analyses:

6.3.3.8.1. Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). **At Weeks 72 and 96, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile**

6.3.3.8.2. Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments **(Weeks 72 and 96)**

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

6.3.3.8.4. Hematology profile: CBC with differential and platelet count

6.3.3.8.5. Plasma HIV-1 RNA

6.3.3.8.6. CD4+ cell count

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

6.3.3.8.8. Serum sample storage for possible additional clinical testing (for subjects who provide consent)

6.3.3.8.9. Evaluations of bone turnover (collected fasted): If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for these evaluations. (**Weeks 72 and 96**)

6.3.3.8.10. Evaluations of inflammation, including but not limited to cystatin-C, IL 6, hs CRP, d-dimer, sCD14, and sCD163 (**Weeks 72 and 96**)

6.3.3.8.11 Evaluations of platelet function, including but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand (**Weeks 72 and 96**)

6.3.3.9. Subjects who meet the criteria for virologic rebound should be managed according to Management of Virologic Failure Section 6.9

6.3.3.10. Document study drug dispensation and accountability for all study drugs dispensed

6.3.3. Treatment Visits (Post Week 96 until the Unblinding Visit and post Unblinding Visit)

After the Week 96 visit, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments have been unblinded, at which point they will return for an Unblinding Visit and will be given the option to receive open-label F/TAF. Study visits are to be completed within ±6 days of the protocol specified visit date unless otherwise specified.

Subjects participating post Week 96 will be required to return for study visits according to the schedule presented in Appendix 2 Study Procedures Table and described in the text below.

6.3.4.1. The following evaluations are to be completed unless otherwise specified: DXA Scans (spine and hip) (**every 24 weeks;** can be performed **≤ 10 days** before study visit)

6.3.4.2. Review of AEs and changes in concomitant medications

6.3.4.3. Completed physical examination (**every 48 weeks**) (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed (at all other visits)

6.3.4.4. Vital signs (blood pressure, pulse, respiration rate, and temperature), including weight

6.3.4.5. 12 lead ECG performed supine (**every 48 weeks**)

6.3.4.6. Urine collection for the following laboratory procedures:

6.3.4.6.1. Urinalysis and urine chemistry

6.3.4.6.2. Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be discontinued

6.3.4.6.3. Urine storage sample for possible additional clinical testing

6.3.4.7. Blood sample collection for the following laboratory analyses:

6.3.4.7.1. Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). **At visits post-Week 96 in which metabolic assessment is to be conducted, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile**

6.3.4.7.2. Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments (**every 24 weeks**).

6.3.4.7.3. Estimated GFR, according to the Cockcroft Gault formula for creatinine clearance

6.3.4.7.4. Hematology profile: complete blood count (CBC) with differential and platelet count

6.3.4.7.5. Plasma HIV-1 RNA

6.3.4.7.6. CD4+ cell count

6.3.4.7.7. Plasma storage samples for virology, safety, and/or PK testing

6.3.4.7.8. Serum storage sample for possible additional clinical testing (for subjects who provide consent)

6.3.4.8. Subjects who meet the criteria for virologic rebound will be managed according to the Management of Virologic Failure Section 6.9

6.3.4.9. Document study drug dispensation and accountability for all study drugs dispensed

6.3.4. Unblinding Visit

Once Gilead Sciences provides unblinded treatment assignments to the Investigators, all subjects will return to the clinic (preferably within 30 days) for an Unblinding Visit. At the Unblinding Visit all subjects will discontinue their blinded study drug and will be given the option to receive open-label F/TAF.

If the F/TAF FDC is not commercially available in a country in which the study is being conducted, subjects who complete the 96 weeks of the study on randomly assigned treatment will be given the option to receive the open- label F/TAF FDC and attend study visits every 12 weeks until it becomes commercially available, or until Gilead Sciences terminates the study in that country.

Subjects who do not wish to receive open-label F/TAF will discontinue their blinded study drug and will return for a 30-Day Follow-up visit following the Unblinding Visit.

Subjects who have discontinued study drug prior to the Unblinding Visit will not be eligible to receive open-label F/TAF; these subjects will be asked to continue attending the scheduled study visits through the Unblinding Visit.

Subjects in certain countries (such as the UK) will stop taking study drug after the Unblinding Visit and return to the clinic 30 days after the completion of study drugs for a 30-day Follow-Up Visit.

The following will be performed at the Unblinding Visit:

6.3.5.1. DXA Scan (spine and hip) required if last scan was acquired > 12 weeks from the date of the Unblinding Visit (can be performed **≤ 10 days** before study visit)

6.3.5.1.1. The DXA scan will be performed once unblinded treatment assignments have been provided and prior to administration of open-label study drug (F/TAF) at the Unblinding Visit. The scan may be performed on the morning of the Unblinding Visit so long as it occurs before open-label study drug dosing

6.3.5.2. Review of AEs and changes in concomitant medications

6.3.5.3. Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)

6.3.5.4. Vital signs (blood pressure, pulse, respiration rate, and temperature), including weight

6.3.5.5. 12-lead ECG performed supine

6.3.5.6. Urine collection for the following laboratory procedures:

6.3.5.6.1. Urinalysis and urine chemistry

6.3.5.6.2. Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will not be able to participate in the open-label rollover study

6.3.5.6.3. Urine storage sample for possible additional clinical testing

6.3.5.7. Blood sample collection for the following laboratory analyses:

6.3.5.7.1. Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)

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

6.3.5.7.3. Hematology profile: CBC with differential and platelet count

6.3.5.7.4. Plasma HIV-1 RNA

6.3.5.7.5. CD4+ cell count

6.3.5.7.6. Plasma storage samples for virology, safety and/or PK testing

6.3.5.7.7. Serum storage sample for possible additional clinical testing (for subjects who provide consent)

6.3.5.8. Document study drug dispensation and accountability for all study drugs dispensed

6.3.5.8.1. Subjects who wish to receive F/TAF will receive F/TAF (200/10 mg or 200/25 mg) based on the third ARV agent in their pre-existing regimen (see Table 5-1).

6.4. Post-treatment Assessments

6.4.1. Early Study Drug Discontinuation (ESDD) Visit

If a subject discontinues study drug prior to the Unblinding Visit, the subject will be asked to return to the clinic within 72 hours of stopping study drug for the Early Study Drug Discontinuation (ESDD) visit. The subject will be asked to continue attending the scheduled study visits through the Unblinding Visit.

At the Early Study Drug Discontinuation Visit, any evaluations showing abnormal results indicating that there is 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 Early Study Drug Discontinuation Visit:

6.4.1.1. Review of AEs and changes in concomitant medications

6.4.1.2. Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)

6.4.1.3. 12-lead ECG performed supine

6.4.1.4. Vital signs (blood pressure, pulse, respiration rate, and temperature), including weight

6.4.1.5. Urine collection for the following laboratory procedures:

6.4.1.5.1. Urinalysis and urine chemistry

6.4.1.5.2. Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test

6.4.1.5.3. Urine storage sample for possible additional clinical testing

6.4.1.5.4. Evaluations of renal tubular function required if last test was acquired > 12 weeks from the date of the ESDD Visit (collected fasted): If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a urine sample for these evaluations

6.4.1.6. Blood sample collection for the following laboratory analyses:

6.4.1.6.1. Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)

6.4.1.6.2. Estimated GFR, according to the Cockcroft Gault formula for creatinine clearance

6.4.1.6.3. Hematology profile: complete blood count (CBC) with differential and platelet count

6.4.1.6.4. Plasma HIV-1 RNA

6.4.1.6.5. CD4+ cell count

6.4.1.6.6. Plasma storage samples for virology, safety and/or PK testing

6.4.1.6.7. Serum storage sample for possible additional clinical testing (for subjects who provide consent)

6.4.1.6.8. HIV-1 genotype/phenotype resistance testing for subjects with confirmed virologic rebound with HIV-1 RNA value ≥ 400 copies/mL

6.4.1.6.9. Evaluations of bone turnover required if last test was acquired > 12 weeks from the date of the ESDD Visit (collected fasted): If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a blood sample for these evaluations

6.4.1.6.10. Evaluations of inflammation required if last test was acquired > 12 weeks from the date of the ESDD Visit, including but not limited to cystatin-C, IL 6, hs CRP, d-dimer, sCD14, and sCD163

6.4.1.6.11 Evaluations of platelet function required if last test was acquired > 12 weeks from the date of the ESDD Visit, including but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand

6.4.1.6.12 Platelet function for substudy subjects (only at selected sites)

6.4.1.7. DXA scan (spine and hip) required if last scan was acquired > 12 weeks from the date of the ESDD Visit. DXA scan can occur up to 10 days after the ESDD Visit

6.4.1.8. Drug accountability

6.4.2. 30 Day Follow-Up Visit

Subjects who complete the study through the Unblinding Visit and who do not wish to receive the open-label F/TAF (including subjects in countries such as the UK) will be required to return to the clinic 30 days after the completion of study drugs for the 30-Day Follow-Up Visit.

Subjects who permanently discontinue study drug during the blinded phase and refuse to continue in the study through the Unblinding Visit will be asked to return to the clinic 30 days after the completion of the Early Study Drug Discontinuation Visit for the 30-Day Follow-Up Visit.

Those subjects who permanently discontinue study drug and continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit <u>will not</u> be required to complete the 30-Day Follow-Up Visit.

For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used. The following evaluations are to be completed at the 30-Day Follow-Up Visit:

6.4.2.1. Review of AEs and changes in concomitant medications

6.4.2.2. Symptom-directed physical examination

6.4.2.3. Vital signs (blood pressure, pulse, respiration rate, and temperature) including weight

6.4.2.4. Urine collection for the following laboratory procedures:

6.4.2.4.1. Urinalysis

6.4.2.4.2. Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test

6.4.2.4.3. Urine storage sample for possible additional clinical testing

6.4.2.5. Blood sample collection for the following laboratory analyses:

6.4.2.5.1. Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)

6.4.2.5.2. Hematology profile: complete blood count (CBC) with differential and platelet count

6.4.2.5.3. Plasma HIV-1 RNA

6.4.2.5.4. CD4+ cell count

6.4.2.5.5. Serum storage sample for possible additional clinical testing (for subjects who provide consent)

At the 30 Day Follow Up Visit, any evaluations showing abnormal results believed to be a reasonable possibility of a 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.

6.5. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degreeFollowing resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.
- 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 subject's best interest
- Therapeutic failure
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 5
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.6. Bone Mineral Density Evaluations

For all subjects excluding those in Germany, dual energy x-ray absorptiometry (DXA) scans will be performed prior to study drug administration at the Day 1, every 24 weeks, Unblinding Visit and the Early Study Drug Discontinuation Visit (if applicable). Scans will cover the spine and hip to measure changes in bone mineral density. DXA scan results will be provided to study sites.

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

6.7. Other Evaluations

6.7.1. Markers of Bone Turnover

For all subjects, blood will be collected for selected evaluations of bone turnover, including C-type collagen sequence (CTX) and procollagen type 1 N-terminal propeptide (P1NP) at Day 1 Visit, Weeks 4, 12, 24, 48, 72, 96 and ESDD (if applicable).

6.7.2. Markers of Renal Tubular Function

For all subjects, urine will be collected for selected evaluations of renal tubular function, including retinol binding protein and beta 2 microglobulin at the Day 1 Visit, Weeks 4, 12, 24, 48, 72, 96 and ESDD (if applicable).

6.7.3. Markers of Inflammation

For all subjects, blood will be collected at Day 1 Visit, Weeks 4, 12, 24, 48, 72, 96 and ESDD (if applicable) for selected evaluations of inflammation, including but not limited to cystatin-C, IL 6, hs CRP, d-dimer, sCD14, and sCD163.

6.7.4. Markers of Platelet Function

For all subjects, blood will be collected at Day 1 Visit, Weeks 4, 12, 24, 48, 72, 96 and ESDD (if applicable) for selected evaluations of platelet function, including but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand. In addition, a subset of subjects will be evaluated for the platelet function (see Section 6.10).

6.8. Blood and Urine Storage

From subjects who provide additional consent, a portion of the blood drawn at all visits (except the Screening Visit and Unscheduled Visits) will be frozen and stored. A portion of urine samples drawn from all subjects at all visits (except the Screening Visit and Unscheduled Visits) will be frozen and stored. These stored blood and urine samples may be used by the Sponsor or its research partners for future testing to learn more about how the study drug has worked against HIV-1 or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without expressed consent of study subjects. At the conclusion of this study, these samples may be retained in storage by Gilead Sciences, Inc. for a period up to 10 years.

6.9. Virologic Failure

Subjects who experience virologic rebound (VR), as defined below, will be considered to have virologic failure.

Subjects will be considered to have virologic rebound if they have confirmed HIV-1 RNA ≥ 50 copies/mL (two consecutive tests) at a scheduled or unscheduled visit.

6.9.1. Management of Virologic Failure

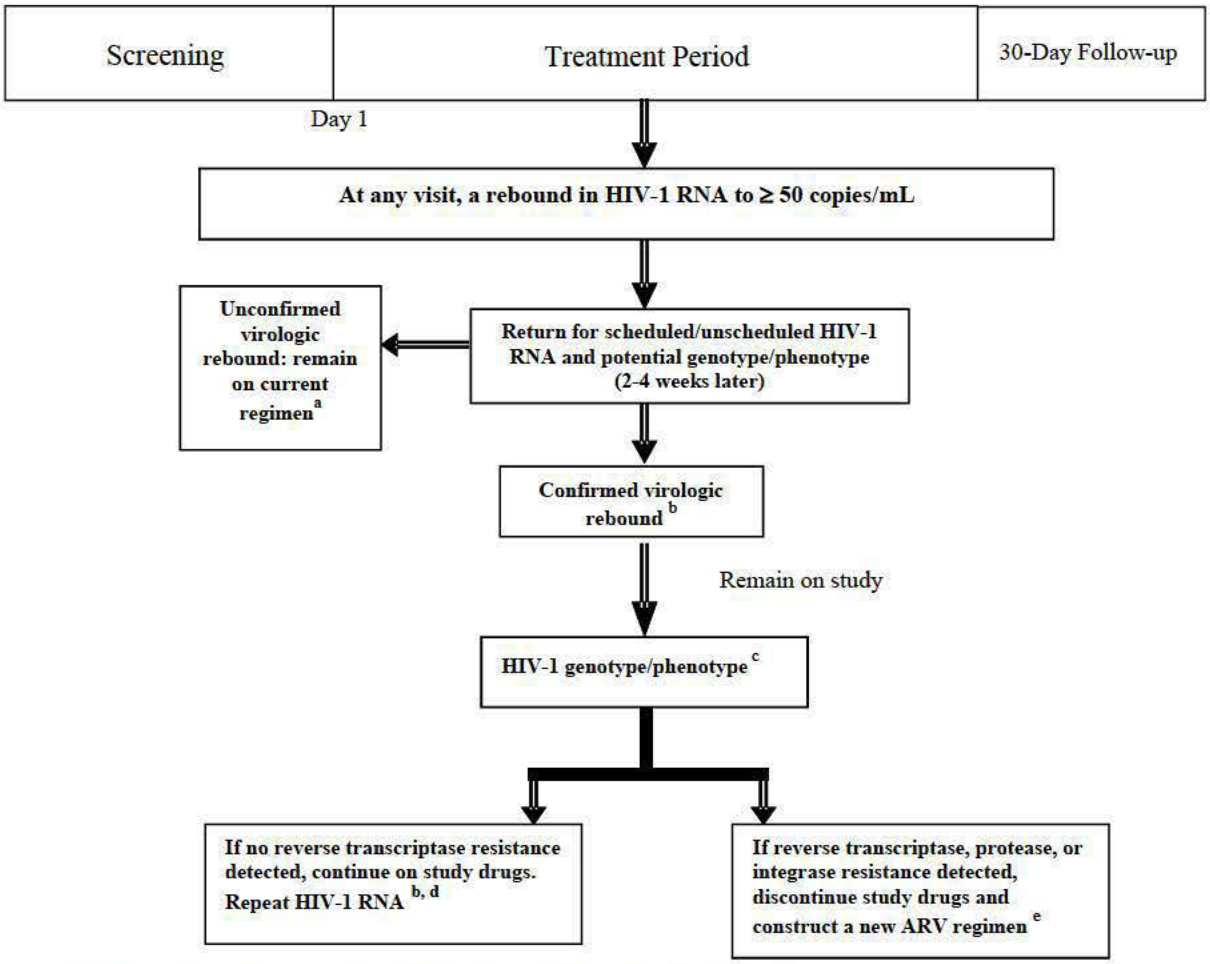
- If the viral load is ≥ 50 copies/mL, HIV-1 RNA should be repeated at a scheduled or unscheduled visit (2-4 weeks after the date of the original test with HIV-1 RNA ≥ 50 copies/mL).
- Upon confirmation of HIV-1 RNA ≥ 50 copies/mL, potential causes of virologic failure should be documented. Assessments should include:
  - — Adherence
  - — Concomitant medication
  - — Comorbidities (for example: active substance abuse, depression, other intercurrent illnesses)
- If virologic failure is confirmed at the scheduled or unscheduled visit and HIV-1 RNA value is ≥ 400 copies/mL, the blood samples from the confirmation visit will be used for HIV-1 genotype/phenotype testing.
- If genotype/phenotype resistance to study drug is documented, study drugs should be discontinued.
- If no resistance is detected from genotype/phenotype testing, subject may remain on study drug and a repeat HIV-1 RNA should be repeated (2-4 weeks from the date of confirmed test with viral load ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug for each individual subject and document this assessment in the on site medical record. Investigators who opt to discontinue study drugs for an individual subject must discuss with the Medical Monitor prior to study drug discontinuation.

6.9.2. Subjects with ≥ 400 copies/mL of HIV-1 in the Absence of VR

Subjects with HIV-1 RNA < 50 copies/mL could subsequently experience unconfirmed blips of HIV-1 RNA ≥ 400 copies/mL. Such subjects will be analyzed for resistance if the unconfirmed rebound happens at Week 48, or at the last visit while receiving study drugs (or within 72 hours of discontinuation of study treatment).

Please refer to Figure 6-1 for the management of subjects who meet the criteria for virologic failure.

Figure 6-1. Schema for Management of Virologic Failure



a If virologic rebound is not confirmed, the subject will remain on their current regimen.
b If virologic rebound is confirmed, and the HIV-1 RNA is ≥ 400 copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase, protease, and, if applicable, integrase resistance) will be analyzed.
c Based on the results of the genotype/phenotype assays, the subject will remain on study drugs or study drugs will be discontinued. If genotyping/phenotyping assay fails, a new ARV regimen may be configured at the discretion of the Investigator.
d If no resistance detected, HIV-1 RNA will be repeated (2-4 weeks later). Investigator reviews study drug continuation/discontinuation options and discuss with Medical Monitor prior to study drug discontinuation
e A new ARV regimen will be configured, at the Investigator's discretion, and the subject will remain in the study

6.10. Platelet Function Substudy

In a subset of patients, platelet function (i.e. reactivity) will be assessed at Day 1 Visit, Weeks 4, 12, and the Early Study Drug Discontinuation Visit (if applicable). The assay to assess platelet function will measure platelet aggregation in response to agonist(s).

In addition, the expression of certain platelet receptors (e.g. glycoprotein VI) may be assessed using flow cytometry. The target sample size for the substudy is up to 80 subjects.

The results will not be provided to the study sites.

A complete description of the procedure performed for the evaluation of platelet reactivity will be provided in a separate laboratory manual.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, 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 medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment 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 such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing 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 (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject 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 subject 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 IMP 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, 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 Section 7.6.

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 IMP therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

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 GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4). For adverse events 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

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the electronic case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

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

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

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, 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 IMP, he/she should promptly document and report the event to Gilead DSPH.

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

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

  Gilead Drug Safety and Public Health (DSPH):
  Fax: +1 650 522 5477
  E-mail: safety_fc@gilead.com

- 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.

- 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 subject identification, maintaining the traceability of a document to the subject identifiers.

- 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 subject's eCRF and the event description section of the SAE form.

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, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (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 investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or 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 Reports

7.5.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.5.2. Instructions for Reporting Special Situations

7.5.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to the Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH.

Gilead DSPH contact information is as follows:

Email: Safety_FC@gilead.com
Fax: +1 (650) 522-5477

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

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 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 3 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 investigational medicinal product 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 subject's safety.

- Clinical events and clinically significant laboratory abnormalities will be graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Refer to Appendix 4).

- 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 investigational medicinal product 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, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.

- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product 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 investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local practice. The subject 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.

Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 3-4 laboratory abnormality (e.g., 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 investigational medicinal product.

7.6.4. Management of Bone Evaluation

As there is uncertainty surrounding the clinical significance and management of decreases in bone mineral density for HIV-1 infected patients, Gilead recommends that any subject 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 practice at the discretion of the investigator.

7.6.5. Management of Hyperbilirubinemia in Patients Receiving Atazanavir

Most patients taking atazanavir sulfate experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronyl transferase (UGT).

As subjects on ATV-containing regimen are expected to have atazanavir-associated hyperbilirubinemia, occasionally up to Grade 4 (> 5 x ULN), the management of graded laboratory abnormality described above in Section 7.6 is not applicable for the management of graded hyperbilirubinemia in these subjects.

However, repeat testing should be done and alternative etiologies (e.g. acute hepatitis B or C) be sought in the following subjects:

1. In those with elevation in conjugated (direct) bilirubin > 1.5 x ULN (i.e. direct hyperbilirubinemia), regardless of the hyperbilirubinemia grade, liver labs (total bilirubin, direct bilirubin, AST, ALT) should be repeated within 7 days of the Investigator being notified of the elevated bilirubin level and be discussed with the Medical Monitor. Thereafter, the management of a subject who continues to have direct bilirubin > 1.5 X ULN, which is deemed as clinically not significant, should be followed according to the clinical judgment of the Investigator.

2. In those with hepatic transaminase elevation, the graded AST or ALT abnormalities should be managed according to Section 7.6.

Dose modification of atazanavir sulfate is not permitted. Subjects who experience unacceptable jaundice/scleral icterus due to atazanavir-associated hyperbilirubinemia can be discontinued from study at the discretion of the Investigator.

7.6.6. Management of Possible Abacavir Hypersensitivity Reaction

Abacavir should not be used in patients known to carry the HLA-B*5701 allele due to increased risk of hypersensitivity reaction, unless no other therapeutic option is available based on the treatment history and resistance testing.

In a clinical study, 3.4 % of subjects with a negative HLA-B*5701 status receiving abacavir developed a hypersensitivity reaction. Therefore, even in the absence of HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

Hypersensitivity reactions are characterized by the appearance of symptoms indicating multi organ system involvement. Almost all hypersensitivity reactions will have fever and/or rash as part of the syndrome. Other signs and symptoms may include respiratory signs and symptoms such as dyspnoea, sore throat, cough, and abnormal chest x-ray findings (predominantly infiltrates, which can be localized), gastrointestinal symptoms, such as nausea, vomiting, diarrhea, or abdominal pain, and may lead to misdiagnosis of hypersensitivity as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis. Other frequently observed signs or symptoms of the hypersensitivity reaction may include lethargy or malaise and musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia). The symptoms related to this hypersensitivity reaction worsen with continued therapy and can be life- threatening. These symptoms usually resolve upon discontinuation of abacavir.

Hypersensitivity reaction symptoms usually appear within the first six weeks of initiation of treatment with abacavir, although these reactions may occur at any time during therapy. Patients should be monitored closely, especially during the first two months of treatment with abacavir.

Regardless of their HLA-B*5701 status, patients who are diagnosed with a hypersensitivity reaction whilst on therapy MUST discontinue study drug immediately and MUST NEVER be restarted. Restarting study drug following a hypersensitivity reaction will result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, study drug must be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medicinal products) {25149}.

7.6.7. Management of Changes in Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (GFR), according to the Cockcroft Gault formula, will be followed post-baseline during the study. All subjects with estimated GFR < 50 mL/min must have serum creatinine and subject's weight measured again within 3 calendar days of receipt of results. If a subject has confirmed estimated GFR < 50 mL/min, the Medical Monitor should be notified and discontinuation of investigational medicinal product should be discussed.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective is:

- To evaluate the efficacy of switching ABC/3TC to F/TAF versus maintaining ABC/3TC in HIV-1 infected subjects who are virologically suppressed on regimens containing ABC/3TC as determined by the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48

The secondary objectives are:

- To evaluate the efficacy, safety and tolerability of two regimens through Week 48 and Week 96

- To evaluate the bone safety of two regimens as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) at Week 48 and Week 96

8.1.2. Primary Endpoint

The primary endpoint is the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot algorithm.

8.1.3. Secondary Endpoint

Secondary endpoints include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 96 as defined by the FDA snapshot analysis

- The percent change from baseline in hip and spine BMD at Week 48 and Week 96

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized

The Randomized analysis set includes all subjects who are randomized into the study. This is the primary analysis set for by-subject listings.

8.2.1.2. Efficacy

8.2.1.2.1. Full Analysis Set (FAS)

The full analysis set (FAS) will include all subjects who (1) are randomized into the study and (2) have received at least one dose of study medication. Subjects will be grouped according to the treatment to which they were randomized.

8.2.1.2.2. Per-Protocol (PP) Analysis Set

The Per-Protocol analysis set will include all subjects who (1) are randomized into the study, (2) have received at least one dose of study medication, and (3) have not committed any major protocol violation, including the violation of key entry criteria. Subjects will be grouped according to the treatment they actually received.

8.2.1.3. Safety

8.2.1.3.1. Full analysis Set (FAS)

The safety analysis set will include all randomized subjects who (1) are randomized into the study and (2) have received at least one dose of study medication. All the data collected up to 30 days after subjects permanently discontinue their study regimen will be included in the safety summaries. Subjects will be grouped according to the treatment they actually received.

8.2.1.4. DXA

8.2.1.4.1. Hip DXA Analysis Set

The Hip DXA analysis set will include all subjects who were randomized and received at least one dose of study medication, and had nonmissing hip BMD value for the Day 1 visit. Subjects will be grouped according to the treatment they actually received.

8.2.1.4.2. Spine DXA Analysis Set

The Spine DXA analysis set will include all subjects who were randomized and received at least one dose of study medication, and had nonmissing spine BMD value for the Day 1 visit. Subjects will be grouped according to the treatment they actually received.

8.2.1.5. Pharmacokinetics

The Pharmacokinetic (PK) analysis set will include all subjects who are randomized and have received at least one dose of study medication and for whom concentration data of any analytes of interest is available. The PK analysis set will be used for analyses of general pharmacokinetics.

8.3. Data Handling Conventions

Appropriate transformations may be applied prior to data summarization and analysis.

8.4. 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 including body weight, height, body mass index, HIV-1 infection, and enrollment distribution by randomization stratum will be summarized.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot algorithm. The primary analysis of the efficacy will be based on the full analysis set (FAS).

The null hypothesis is that the proportion of subjects with HIV-1 RNA < 50 copies/mL (as defined by the FDA snapshot algorithm) at Week 48 in the Treatment Arm 1 is at least 10 percentage points lower than the response rate in the Treatment Arm 2; the alternative hypothesis is that the response rate in Treatment Arm 1 is less than 10% lower than that in Treatment Arm 2.

Non-inferiority will be assessed using the conventional confidence interval approach. The point estimate of treatment difference (F/TAF arm – FTC/TDF arm) and the associated two-sided 95% confidence interval will be constructed using normal approximation method based on stratum-stratified Mantel-Haenszel proportions, where the stratification factor is the third agents (boosted protease inhibitors vs. other agents).

Once non-inferiority of F/TAF treatment regimen to FTC/TDF treatment regimen is established, the lower bound of the 95% CI will be compared to 0; if the lower bound of the 95% CI is greater than 0, then superiority of F/TAF over FTC/TDF will be established.

8.5.2. Secondary Analyses

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96, as defined by the FDA snapshot algorithm, will be analyzed using the same method as for the primary efficacy endpoint.

8.6. Safety Analysis

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

All safety data collected on or after the date that study regimen was first taken up to the date of last dose of study regimen plus 30 days will be summarized by treatment group according to the study regimen received. Data for the pretreatment period and the period post the date of last dose of study regimen plus 30 days will be included in data listings.

8.6.1. Extent of Exposure

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

Duration of exposure to IMP will be expressed as the number of weeks between the first and last dose of the study regimen, inclusive, regardless of temporary interruptions in study regimen administration and summarized by treatment.

Dosing information for individual subjects will be listed.

8.6.2. Adverse Events

Clinical and laboratory adverse events 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. A treatment-emergent adverse event will be defined as any adverse event that begins on or after the date of first dose of IMP study regimen up to 30 days after the date of last dose of IMP study regimen or any AEs leading to study regimen discontinuation

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC and PT) will be provided by treatment group. Additional summaries will include summaries for adverse events by grade, Investigator's assessment of relationship to IMP, and effect on IMP dosing.

On an ongoing basis adverse events will be reviewed for events that might meet the definition of Category C events that are indicative of an AIDS-Defining Diagnoses. The Gilead medical personnel will review the possible Category C events and approve the events that meet the definition. Those events that do meet the Category C definition of an AIDS-Defining Diagnosis will be listed.

A listing of Category C, AIDS-Defining Diagnosis, can be found in Appendix 6.

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the grading scheme defined in Grading of laboratory abnormalities provided in Appendix 4.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to and including the date of last dose of study regimen plus 30 days, will be summarized by treatment group. If baseline data are missing, then any graded abnormality (i.e. 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 regimen or after the subject has been discontinued from treatment plus 30 days will be included in a data listing.

8.6.4. Bone Mineral Density

Percentage change from baseline in hip and spine BMD will be summarized. The difference in percentage change at Week 48 from baseline between the two treatment arms will be tested using ANOVA model, including the third agent stratum (boosted protease inhibitors vs. other agents) as a fixed effect.

Missing post-baseline values for BMD will be imputed using last observation carried forward (LOCF).

8.6.5. Other Safety Evaluations

Safety ECGs will be summarized for subjects in the Safety Analysis Set. Number and percent of subjects with abnormal safety ECG will be summarized by visit.

8.7. Pharmacokinetic Analysis

The PK concentration data of individual analytes may be explored.

8.8. Analysis of Evaluations of Bone Turnover, Renal Tubular Function, and Inflammation

The observed values and changes from baseline in these evaluations will be summarized by treatment group and visit using descriptive statistics, based on the safety analysis set. The difference in change from baseline in these evaluations between two treatment arms will be tested using van Elteren method, stratified by the third agents (boosted protease inhibitors vs. other agents).

The skewness of the data will be examined and a natural log transformation may be applied especially for exploratory analysis. If any transformation is applied, the changes from baseline will be reported in original units (ie, back transformation will be applied to the generated statistics, eg: fold-change from baseline may be reported instead of change from baseline).

8.9. Sample Size

A total of 500 HIV-1 infected subjects, randomized in a 1:1 ratio to two arms (250 subjects per arm), achieves at least 90% power to detect a non-inferiority margin of 10% in Week 48 response rate (HIV-1 RNA < 50 copies/mL as defined by the FDA snapshot algorithm) difference between the two groups. For sample size and power computation, it is assumed that both treatment arms have a response rate of 0.87, that a non-inferiority margin is 0.10, and that the significance level of the test is at a one-sided 0.025 level.

8.10. Independent Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data, and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design, and the collection or analysis of data.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

An analysis for the Week 12 IDMC meeting will be conducted after the first 250 subjects are enrolled and complete Week 12, and subsequently when all enrolled subjects complete Week 24 of the study. Gilead Sciences does not have a prior intent to ask the IDMC to review Weeks 48 results and to consider early termination of the study even if there is early evidence of favorable efficacy.

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), International Conference on Harmonisation (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 subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The Investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators", 21 CFR, part 50, "Protection of Human Subject", and 21 CFR, part 56, "Institutional Review Board".

The Investigator and all applicable Sub-Investigators will comply with 21 CFR, Part 54, "Financial Disclosure by Investigators", 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 Sub-Investigator's) participation in the study. The Investigator and Sub-Investigator 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 subject 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, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject 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 subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

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- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject 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 [or] IEC, or laboratory. Laboratory specimens must be labeled in such as way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject 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 investigator brochure, this protocol, eCRF, the IMP, 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 two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB [or] IEC and governmental approval with correspondence, informed consent, 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 subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject 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 IMP, including dates of dispensing and return;
- Record of all adverse events 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, United States, 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 subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator 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 (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. 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

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP 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 IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

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

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

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs [or] 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 subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB [or] IEC in accordance with local requirements and receive documented IRB [or] 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. 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, e.g. 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 trial 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 subject 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 subjects' interests.

10. REFERENCES

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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 3b, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed on Regimens containing ABC/3TC

GS-US-311-1717 Original Protocol: 11 March 2015

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

Moupali Das PPD

Moupali Das, MD, MPH (Printed)
Medical Monitor

3/11/2015
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 _____

Appendix 2. Study Procedures Table

Study Procedure	Screen[a]	Day 1[b]	End of Week[c]										Post-Week 96[d]	Unblinding Visit[v]	30 Day Follow-up[e]	ESDD[f]
			4	8	12	24	36	48	60	72	84	96	Every 12 Weeks			
Informed Consent	X															
Medical History	X															
Concomitant Medications	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
Complete Physical Exam	X	X				X		X		X		X	X[g]	X		X
Symptom-Directed Physical Exam[h]			X	X	X		X		X		X		X		X	
12-Lead ECG (performed supine)	X							X				X	X[z]	X		X
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[y]	X
Height	X															
Urinalysis and Urine Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[aa]	X
Urine Storage Sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Screen[a]	Day 1[b]	End of Week[c]										Post-Week 96[d]	Unblinding Visit[v]	30 Day Follow-up[e]	ESDD[f]
			4	8	12	24	36	48	60	72	84	96	Every 12 Weeks			
Serum Pregnancy Test[i]	X															
Chemistry Profile[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Metabolic Assessments[k]		X				X		X		X		X	X[r]	X		
Estimated GFR[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology Profile[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA[x]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma Sample Storage[m]		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Serum Storage Sample[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Whole Blood Storage Sample[bb]		X														
Whole Blood Sample for PBMCs			X[dd]													
HBV Serology	X															

Study Procedure	Screen[a]	Day 1[b]	End of Week[c]										Post-Week 96[d]	Unblinding Visit[v]	30 Day Follow-up[e]	ESDD[f]
			4	8	12	24	36	48	60	72	84	96	Every 12 Weeks			
HCVAb Serology[n]		X														
HIV-1 Genotype/Phenotype[o]																X[o]
Single PK Sample[p]				X	X	X	X									
Post-dose PK Sample[q]			X					X								
Platelet substudy blood sample		X[ee]	X[ee]		X[ee]											X[ee]
DXA Scan (spine & hip)[s]		X				X		X		X		X	X[s]	X		X
Evaluations of bone turnover, renal tubular function, inflammation and platelet function[t]		X	X		X	X		X		X		X				X[t]
Randomization		X														
Study Drug Dispensation and Accountability		X	X	X	X	X	X	X	X	X	X	X	X	X[cc]		X[u]

a Evaluations to be completed within 30 days prior to Day 1 Visit.

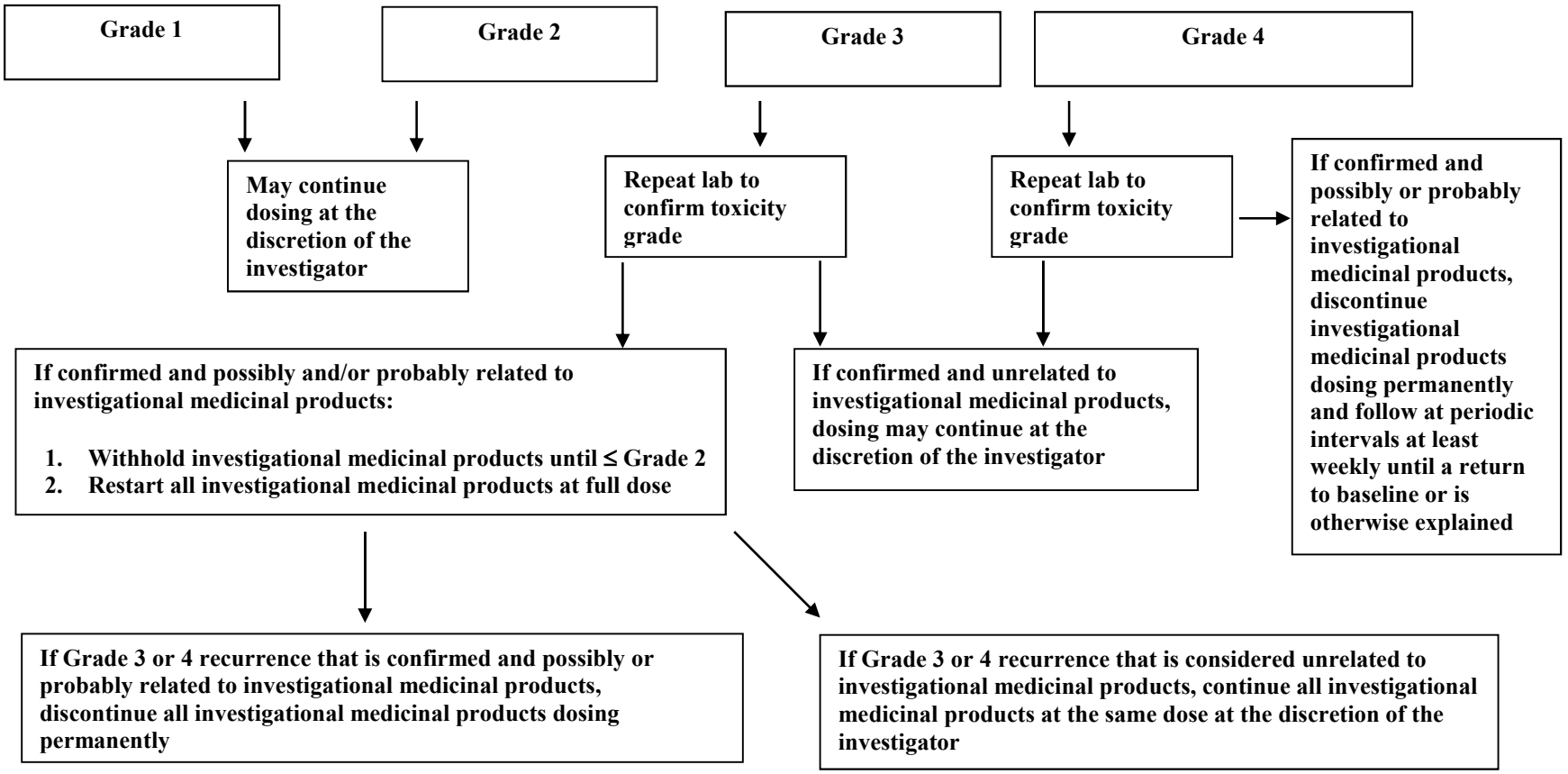
b Subjects will be dispensed study drug on the Day 1 Visit; initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit. F/TAF, ABC/3TC, placebo-to-match F/TAF and placebo-to-match ABC/3TC will be provided by the Sponsor.

c All study visits are to be scheduled relative to the Day 1 Visit date. Visit windows are ± 2 days of the protocol specified date through Week 12, ± 6 days of the protocol specified date through Week 36, and all other study visits except Week 48 and Week 96. Weeks 48 and 96 visit windows are ± 6 weeks of the protocol specified date.

d Study visits are to be completed within ± 6 days of the protocol-specified visit date unless otherwise specified.
e Only required for those subjects who do not wish to continue to participate after the Unblinding Visit, all subjects in countries such as the UK , or those subjects who permanently discontinue study drug and do not continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.
f Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through Unblinding visit even if the subject discontinues study drug.
g Complete physical examination every 48 weeks (urogenital/anorectal exams will be performed at the discretion of the Investigator).
h Symptom-directed physical examination as needed.
i Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
j Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) At Day 1, Weeks 24, 48, 72, 96, and every 24 weeks post week 96, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.
k Metabolic Assessments: Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
l CBC with differential and platelet count.
m Plasma storage samples for virology, safety, and/or pharmacokinetic analysis. Serum storage samples for possible additional clinical testing.
n If the antibody test result is positive, HCV RNA test will be performed to confirm HCV viremia
o HIV-1 genotype/phenotype resistance testing only conducted for subjects with confirmed virologic failure with HIV-1 RNA value ≥ 400 copies/mL. Subjects should be managed according to the Virologic Failure Schema (Section 6.9). HIV-1 genotype/phenotype sample collection to occur if subjects HIV-1 RNA lab values meet the criteria described in this section.
p At Weeks 8, 12, 24 and 36, subjects will have a single PK sample collected as part of their safety laboratory blood draws anytime pre-or post-dose.
q At the Weeks 4 and 48 visits only, PK sample will be collected 15 minutes to 4 hours post-dose, following observed in-clinic dose.
r Metabolic assessments post week 96 will be performed every 24 weeks.
s DXA scan to be performed in all eligible subjects except for those in Germany, prior to study drug administration at Day 1 Visit. DXA scan also to be performed at visits every 24 weeks up to Wk 96 and every 24 weeks Post-Wk 96 (can be performed ≤ 10 days before study visits), at Unblinding Visit and the ESDD visit (if the last scan was acquired > 12 weeks from the date of the ESDD Visit).
t Blood for selected evaluations of bone turnover, including C-type collagen sequence (CTX) and procollagen type 1 N-terminal propeptide (P1NP), inflammation including cystatin-C, IL-6, hs-CRP, d-dimer, sCD14, and sCD163, and platelet function including soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand will be collected. Urine for selected evaluations of renal tubular function, including retinol binding protein, and beta-2-microglobulin, will be collected. Required for ESDD visit if last test was > 12 weeks from ESDD visit. Samples for bone turnover and renal tubular function will be collected fasted. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for these evaluations and provide a urine sample for these evaluations.
u Drug accountability only; study drug will not be dispensed at this visit.
v At the Unblinding Visit, subjects (except in certain countries such as UK) will be given the option to receive open-label F/TAF FDC and attend study visits every 12 weeks until it becomes commercially available, or until Gilead Sciences terminates the study in that country.
w Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
x If the HIV-1 RNA value is ≥ 50 copies/mL a retest should be collected at a scheduled or unscheduled visit, 2-4 weeks after the date of the original test (except for screening and baseline results).
y Weight only

z 12-lead ECG performed supine every 48 weeks post week 96
aa Urinalysis only
bb Sample collected at Day 1 visit is for virology assessments.
cc F/TAF will be provided to all subjects who would like to receive open-label F/TAF (except in certain countries such as UK). Study drug will not be provided to subjects who wish to discontinue participation at this visit.
dd Single whole blood sample collection **(Week 4 only)**: PBMC sample processing will be performed by the central laboratory; TFV-DP concentrations in PBMCs will be determined.
ee Sample only collected for platelet substudy subjects at selected sites.

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Version: 18June2012

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days** **Infant, 2 – ≤ 7 Days** **Infant, 1 Day**	1000 to 1300/mm^3 1.00 to 1.30 GI/L 1250 to 1500/mm^3 1.25 to 1.50 GI/L 4000 to 5000/mm^3 4.00 to 5.00 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L 1000 to < 1250/mm^3 1.00 to < 1.25 GI/L 3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L 750 to < 1000/mm^3 0.75 to < 1.00 GI/L 1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 500/mm^3 < 0.50 GI/L < 750/mm^3 < 0.75 GI/L < 1500/mm^3 < 1.50 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
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 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 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 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x 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%

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	146 to 150 mEq/L 146 to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia	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	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
Hypoglycemia **Adult and Pediatric ≥ 1 Month** **Infant, < 1 Month**	 55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	 40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	 30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	 < 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 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
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	 7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	 7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	 6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	 < 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L 11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L > 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L > 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L > 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 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** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to 3.5 mg/dL 0.96 to 1.12 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia	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
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	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
LDL (Fasting)	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
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

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	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 Covance Laboratory, 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 (e.g., 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) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization (other than ER visit) indicated Life-threatening consequences (e.g., 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 with nonurgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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, e.g., 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, e.g., Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., 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 two 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 [e.g., tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., 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 (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., 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 (e.g., 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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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 (e.g., 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 (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (e.g., 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 (e.g., 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 (e.g., hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (e.g., 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 (e.g., 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
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental 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 weak-ness 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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (pre-existing) 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 pre-existing 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 (e.g., severity or focality)	Seizures of any kind that are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., 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

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 [e.g., 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 **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	Necrosis (involving dermis and deeper tissue) **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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., myxedema coma)
Lipoatrophy (e.g., 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 (e.g., 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 antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial 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 (e.g., septic shock)

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations

1. Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

The risks of treatment with the study drug during pregnancy have not been evaluated. Pregnancy must be excluded before the start of treatment with study drug and prevented thereafter by reliable contraceptive methods. Pregnancy tests will be performed regularly throughout this study (Refer to Appendix 2). If females are using hormonal agents for contraception, the safety and/or efficacy may be affected by possible drug-drug interaction. However, if females are using hormonal agents for contraception, the hormonal agent may be continued and a non-hormonal method (or methods) must be used concurrently. If females utilize hormonal agents as one of their contraceptive methods, it is required that the same hormonal method be used for at least 3 months before study dosing.

Please refer to the latest version of the Investigator's Brochure for additional information. Additional pregnancy precaution requirements may be indicated based on third agent selection (refer to the relevant local label) and should be implemented at the discretion of the investigator.

2. Definition of Female of Childbearing Potential

For the purposes of this study, a female subject of childbearing potential is a non-menopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.

A female subject may be considered menopausal in either of the following conditions:

- Surgical menopause: Appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries and occurring at the age at which the procedure was performed)
- If age > 54 years and with cessation for ≥12 months of previously occurring menses due to ovarian failure.
- Women ≤ 54 years of age and with the absence of normal menses will be considered to be of childbearing potential.

3. Contraceptive Requirements

Male subjects and female subjects of childbearing potential who engage in intercourse must agree to utilize protocol specified methods of contraception from the Screening/enrollment visit (for females) or first dose visit (for males) and for 30 days following the last dose of study drug. Female study subjects who are not heterosexually active must provide periodic confirmation of continued abstinence from heterosexual intercourse and regular pregnancy testing while taking study medication. The Investigator will counsel subjects on the protocol specified method(s) for

avoiding pregnancy in case the subject chooses to engage in heterosexual intercourse. These methods are recommended due to the low failure rate (i.e., less than 1% per year).

Protocol specified contraceptive methods are as follows: (1) a combination of one hormonal method and one barrier method; (2) use of an intrauterine device (IUD) or tubal sterilization (See Appendix Table 1 below) or (3) complete abstinence from intercourse. Periodic abstinence from intercourse (for example: calendar, ovulation, symptothermal, post-ovulation methods) is not permitted.

Acceptable hormonal methods include injectable progesterone, progesterone implants, combination oral contraceptives, transdermal contraceptive patch, and vaginal ring. Acceptable barrier methods include diaphragm, cervical cap, and the male condom. Female subjects must use either a hormonal method or a barrier method if the partner has a vasectomy. If a subject has undergone tubal sterilization or has had a Copper T 380A IUD or LNg 20 IUD inserted, no other contraception is needed;

If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after microinsertion. Prior to verification, Essure is not considered a reliable form of contraception and the contraception methods described below must be used. Female subjects who utilize hormonal contraceptives as one of their birth control methods must have used the same method for at least 3 months before study dosing.

Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Day 1 prior to receiving the first dose of study drug.

Appendix Table 1. Protocol Specified Contraceptive Methods

	Combination Methods	
Methods to Use by Themselves	**Hormone Methods (choose one and use with a barrier method)**	**Barrier Methods (choose one and use with a hormone method)**
Intrauterine Devices (IUDs) • Copper T 380A IUD • LNg 20 IUD **Tubal Sterilization**	**Estrogen and Progesterone** • Oral contraceptives • Transdermal patch • Vaginal ring **Progesterone** • Injection • Implant	• Diaphragm OR Cervical cap • Male condom (without spermicide)
	Partner's vasectomy must be used with a hormone or barrier method.	

The Investigator will counsel all subjects on the most effective method(s) for avoiding pregnancy during the study.

Male subjects must agree to use condoms during heterosexual intercourse and avoid sperm donation while enrolled in the study and for at least 30 days after administration of the last dose of study medication.

Use of condoms (except for lambskin) has been proven to decrease the risk of transmission of HIV and other sexually transmitted diseases. The use of spermicide is not recommended if the subject or subject's partner is infected with HIV.

4. Procedures to be Followed in the Event of Pregnancy

Female subjects will be instructed to notify the Investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and seek the investigator's advice regarding action required with the study drug immediately.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.5.2.

Appendix 6. Definitions of HIV-1 Related Disease (CDC Guidelines)

Category B: Symptomatic Conditions in HIV-Infected Subjects

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting > 1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one Dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

Category C: AIDS-Defining Diagnoses

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month duration)
- Cytomegalovirus disease (other than liver, spleen or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related

- Herpes simplex: chronic ulcer(s) (> 1 month duration); or bronchitis, pneumonitis or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Myobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, pulmonary or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome attributed to HIV infection

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