CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Abacavir/Lamivudine (ABC/3TC) plus a Third Antiretroviral Agent to the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed HIV-1 Infected Adult Subjects	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	111007	
EudraCT Number:	2015-002711-15	
Clinical Trials.gov Identifier:	TBD	
Indication:	HIV-1 Infection	
Protocol ID:	GS-US-292-1823	
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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Study Title:	A Phase 3b, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Abacavir/Lamivudine (ABC/3TC) plus a Third Antiretroviral Agent to the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed HIV-Infected Adult Subjects
IND Number:	111007
EudraCT Number:	2015-002711-15
Clinical Trials.gov Identifier:	TBD
Study Centers Planned:	Approximately 55 centers in Europe and North America
Objectives:	The primary objective of this study is: • To evaluate the efficacy of switching to E/C/F/TAF FDC relative to continuing on a baseline regimen consisting of ABC/3TC plus a third antiretroviral agent in maintaining HIV-1 RNA < 50 copies/mL at Week 24 (using FDA snapshot algorithm) in virologically suppressed, HIV-1 infected adult subjects The secondary objectives of this study are: • To evaluate the proportion of subjects maintaining virological response (defined as HIV-1 RNA < 50 copies/mL, FDA snapshot analysis) at Weeks 12 and 48 • To evaluate changes from baseline in CD4+ cell counts at Weeks 24 and 48 • To evaluate the safety and tolerability of the two treatment groups over 24 and 48 weeks

Study Design:	Randomized, open-label, multicenter study to evaluate the safety and efficacy of switching from ABC/3TC plus a third antiretroviral agent to E/C/F/TAF FDC in virologically suppressed, HIV-1 infected adult subjects. Subjects will be randomized in a 2:1 ratio to one of following treatment groups. Randomization will be stratified by age (< 60 years or ≥ 60 years): • **Treatment Group 1:** Switch from ABC/3TC plus a third antiretroviral agent to E/C/F/TAF FDC (n = 200) • **Treatment Group 2:** Continue on the current regimen of ABC/3TC plus a third antiretroviral agent for 24 weeks followed by a delayed switch to E/C/F/TAF FDC (n = 100)
Number of Subjects Planned:	Approximately 300 subjects. At least 40 subjects ≥ 60 years old will be enrolled.
Target Population:	HIV-1 infected subjects ≥ 18 years old who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ABC/3TC containing regimen plus a third agent for ≥ 6 consecutive months prior to screening.
Duration of Treatment:	A 42 day screening period followed by 48 weeks on study and a 30 Day Follow-Up visit after completion of study
Diagnosis and Main Eligibility Criteria:	HIV-infected adult subjects who meet the following criteria will be given the option to participate in the study: • Currently receiving ABC/3TC plus a third antiretroviral (ARV) agent for ≥ 6 consecutive months preceding the screening visit. Subject must be on their first or second ARV regimen. Allowed third antiretroviral agents include LPV/r, ATV+RTV, ATV+COBI (or ATV/COBI FDC), DRV+RTV, DRV + COBI (or DRV/COBI FDC), EFV, RPV, NVP, ETR, RAL or DTG • Documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 months preceding the screening visit (measured at least twice using the same assay). In the preceding 6 months prior to screening, one episode of "blip" (HIV-1 RNA > 50 and < 400 copies/mL) is acceptable, only if HIV-1 RNA is < 50 copies/mL immediately before and after the "blip". • Plasma HIV-1 RNA < 50 copies/mL at screening visit

	• Documented historical genotype prior to starting initial ARV therapy (ART) showing no known resistance to tenofovir disoproxil fumarate (TDF) or emtricitabine (FTC), including, but not limited to the presence of reverse transcriptase resistance mutants K65R, M184V/I, or thymidine analog-associated mutations (TAMs) (TAMs are: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R). If a historical genotype is not available, subject will have proviral genotype analysis for archived resistance at screening visit. • Adequate renal function defined as having an estimated glomerular filtration rate of ≥ 30 mL/min as calculated by Cockcroft-Gault ($eGFR_{CG}$)
Study Procedures/ Frequency:	After screening, study visits will occur at Day 1 and Weeks 4, 8, 12, 24, 36, and 48. Subjects in Treatment Group 2 will also have a study visit at Weeks 28 and 32, which are four and eight weeks after switching to the E/C/F/TAF FDC, respectively. Adverse events and concomitant medications will be assessed at each visit. Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count, assessment of adverse events and concomitant medications and complete or symptom directed physical examinations will be performed at all study visits. Calculated creatinine clearance, fasting glucose, hematology, serum chemistry, urine chemistry and urinalysis tests will be performed at all visits. Fasting lipid panel (total cholesterol (TC), high density and low density lipoproteins (HDL, LDL), and triglycerides (TG)) will be collected at Day 1, and Weeks 12, 24, 36 (Treatment Group 2 subjects only) and 48. Blood and urine for selected evaluations of bone and renal safety, inflammation, platelet function, and coagulation will be collected at Day 1, Weeks 4, 12, 24 and 48 (all subjects) and also at Weeks 28 and 36 for Treatment Group 2 subjects only.
Test Product, Dose, and Mode of Administration:	Elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF) FDC administered orally once daily with food
Reference Therapy, Dose, and Mode of Administration:	ABC/3TC (abacavir 600 mg / lamivudine 300 mg) plus a third antiretroviral agent for oral administration according to prescription

Criteria for Evaluation:

Safety:	The safety and tolerability of the treatment regimens will be assessed with adverse event and clinical laboratory tests (including selected evaluations of bone and renal safety, inflammation platelet function and coagulation) at Weeks 24 and 48.
Efficacy:	Primary endpoint: • HIV-1 RNA < 50 copies/mL at Week 24 (FDA snapshot analysis) Secondary endpoints: • HIV RNA < 50 copies/mL at Weeks 12 and 48 (FDA snapshot analysis) • Changes in CD4+ cell count at Weeks 24 and 48
Health Related Questionnaires:	Health related questionnaires will be administered, including the Adherence Visual Analogue Scale (VAS), HIV Treatment Satisfaction (HIVTSQ), EQ-5D, Medical Outcome Study Short Form-36 (SF-36), and Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-F).
Statistical Methods:	The primary evaluation of the FDA defined snapshot endpoint at Week 24 will be evaluated by constructing a two-sided exact 95% confidence interval for the difference in treatment group response rates (E/C/F/TAF FDC minus control) to determine if the lower bound is greater than -0.120. Superiority will be declared (p-value will be calculated) if the lower bound of the 95% confidence interval is greater than 0. Descriptive statistics will be provided for the secondary endpoints including CD4, adverse events and clinical laboratory data by treatment groups.
Sample Size:	With 200 subjects randomized to switch to the E/C/F/TAF FDC at Day 1 and 100 subjects randomized to the delayed switch group, the lower limit of the observed one sided 97.5% confidence interval will be expected to be greater than -0.120 (ie, non-inferiority margin of 12%) with > 90% power when the percentage of responders in both treatment groups for the primary endpoint is at least 90% at Week 24. Subjects ≥ 60 years of age will be included in a pre-planned cross-study, pooled analysis of the safety, efficacy and effect on cardiovascular and inflammatory biomarkers E/C/F/TAF FDC in Studies GS-US-292-1823 and GS-US-292-1826.

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	artioventricular
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
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
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
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
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
INR	international normalized ratio

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) Single Tablet Regimen (STR)
STR	single tablet regimen
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 maximum observed concentration of drug
UGT	uridine glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
VR	virologic rebound
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 that is of major public health interest around the world. There are 35 million people worldwide and approximately 1.1 million people in the US living with HIV-1 {15971}, {19661}. Within Western and Central Europe, it is estimated that there are over 900,000 individuals living with HIV and 131,000 new infections in 2012 {35257}.

If left untreated or suboptimally treated, HIV infection is characterized by deterioration in immune function, the subsequent occurrence of opportunistic infections and malignancies, ultimately resulting in death. Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral therapy (HAART); the introduction of HAART was associated with a dramatic decrease in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality {27881}, {24156}, {8284}.

The primary goals of ARV therapy for HIV-1 infection are to reduce HIV-associated morbidity and prolong the duration and quality of life, restore and preserve immunologic function, maximally and durably suppress plasma HIV viral load, and prevent HIV transmission. The DHHS guidelines list emtricitabine/tenofovir DF (FTC/TDF) as a preferred nucleos(t)ide reverse transcriptase inhibitor NRTI/NtRTI backbone in combination with either cobicistat-boosted elvitegravir [EVG/COBI] administered as EVG/COBI/FTC/TDF, raltegravir, dolutegravir or darunavir/ritonavir as an initial ARV regimen {34898}. Although HAART has dramatically improved the prognosis of patients infected with HIV-1, eradication of the virus is not possible with currently available therapies. Long-term viral suppression and prevention of drug resistance are goals of successful therapy. In regimens of comparable efficacy, the total pill burden, dosing frequency, and concerns about safety and side effects are generally the most significant obstacles to achieving high adherence {4266}, {4256}, {34898}.

Tenofovir disoproxil fumarate (TDF) is a preferred NRTI among recommended regimens for treatment-naïve HIV-positive patients, but is associated with nephrotoxicity and reduced bone mineral density {21769}. Lifelong antiretroviral treatment and the increasing comorbidities being recognized and treated in HIV-positive patients creates an urgent need to improve the safety profile of regimens that most effectively suppress HIV replication. Tenofovir alafenamide (TAF) is novel oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. Gilead has coformulated TAF with the integrase strand transfer inhibitor elvitegravir (EVG), cobicistat (COBI), and emtricitabine (FTC) into a fixed-dose combination (FDC). Compared to TDF, the use of TAF in the E/C/F/TAF FDC provides enhanced lymphatic delivery of tenofovir, resulting in higher intracellular levels of the active phosphorylated moiety tenofovir-diphosphate, and lower systemic circulating levels of tenofovir. These features translate into an improved tolerability and safety profile, especially with respect to renal and bone safety {34827}.

1.2. Tenofovir Alafenamide (TAF, GS-7340)

1.2.1. General Information

Tenofovir alafenamide (GS-7340, TAF, or L-Alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]/phenoxyphosphinyl]-, 1-methylethyl ester) is an investigational oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. TFV 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.

For further information on TAF, refer to the current investigator's brochure for E/C/F/TAF FDC.

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. 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.

1.2.2.2. 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 post-dosing with reversibility

beginning by 6 hours after dosing. The NOEL for gastrointestinal motility was 100 mg/kg. The IC_{50} for the inhibitory effect of TAF fumarate (GS-7340-03) on hERG potassium current was estimated to be greater than 10 μM.

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.

1.2.3. Nonclinical Pharmacokinetics

All nonclinical PK experiments 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).

Key results from nonclinical absorption, distribution, metabolism, and excretion studies of TAF are as follows:

- Following oral administration in dogs and monkeys, TAF demonstrated rapid absorption, with peak plasma concentrations between 0.25 and 0.5 hours. Thereafter, TAF plasma concentrations declined rapidly with a terminal half-life of less than 1 hour. Tenofovir alafenamide exposure (C_{max} and AUC values) was nonlinear with dose and greater than expected with increasing dose. Repeat-dose studies in rats and monkeys showed no change in pharmacokinetics over time.

- 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.

- Following oral administration of [^{14}C]-radiolabeled TAF to dogs, a mean total recovery of radioactivity at 24 hours of 63% was demonstrated. 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, peripheral blood mononuclear cells (PBMCs), liver, large intestine, and bile. Additional studies in dogs, TFV concentrations in PBMCs following oral administration of TAF were approximately 50-fold greater than observed in plasma, with an estimated $t_{½}$ of greater than 24 hours.

- The major route of elimination of TAF-related radioactivity was via feces, with approximately 35% of the dose recovered in feces through 48 hours postdose. The primary route of elimination of TFV is renal excretion of unchanged drug based on IV studies of TFV.

- Tenofovir alafenamide has been found to be a substrate for intestinal efflux transport and in nonclinical studies its intestinal absorption was increased by the transport inhibitor cyclosporin A.

- No significant inhibition of human drug metabolizing cytochrome P450 (CYP) enzymes, uridine diphosphate glucuronyltransferase (UGT) 1A1 or transporters including P-glycoprotein, breast cancer resistance protein, organic anion-transporting polypeptide (OATP)1B1 and OATP1B3 was observed with TAF in vitro.

- Tenofovir alafenamide did not activate human pregnane X receptor (hPXR) or aryl hydrocarbon receptor (AhR).

- Tenofovir alafenamide was not a substrate for drug-metabolizing CYP enzymes except for CYP3A4, which metabolized the compound slowly.

1.2.4. Nonclinical Toxicology

Key results from nonclinical toxicology studies of TAF are as follows:

- Based on TFV exposure, the no observed adverse effect levels (NOAELs) in the 6-month rat, 9-month dog, and 1-month monkey studies provide 14-, 4-, and 22-fold safety margins, respectively, for a human dose of 25 mg/day.

- In chronic studies in rats, bone (atrophy of metaphyseal cancellous bone) and kidneys (karyomegaly) were the primary target organs after 26 weeks of treatment with TAF 100 mg/kg/day; however, effects were not seen at lower doses. Tenofovir alafenamide 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 at doses up to TAF 18/12 mg/kg/day (the high dose was reduced from 18 to 12 mg/kg/day due to the occurrence of death, severe clinical signs and reduced body weight), the primary target organs were kidney (slight to moderate renal tubular degeneration and karyomegaly) and bone (decreased bone mineral density [BMD] in metaphyseal cancellous bone).

- Tenofovir alafenamide had no discernable electrocardiograph effect at the low dose of 2 mg/kg/day. There was some evidence at 6 and 18/12 mg/kg/day for an effect to slightly prolong PR intervals.

- After 9 months of treatment, some dogs administered the highest dose of TAF (18/12 mg/kg/day) had minimal mononuclear cell infiltration in the posterior uvea, considered secondary to general debilitation; this finding did not occur in animals given lower doses and it has not occurred in other animal studies.

- There were no clear treatment-related effects observed in monkeys following 28 days of TAF treatment at 3 and 30 mg/kg/day, including no changes in mitochondrial function and mitochondrial DNA (mtDNA) content in the liver, kidney, and skeletal muscle, and characterization of lymphocyte populations.

- Tenofovir alafenamide was not genotoxic in either in vitro or in vivo assays. Tenofovir alafenamide had no adverse effects on male or female fertility parameters in rats. There was no effect on fetal viability or fetal development in pregnant rats administered doses of TAF up to 250 mg/kg/day or in pregnant rabbits administered TAF up to 100 mg/kg/day; the highest doses were maternally toxic.

1.2.5. Clinical Trials of E/C/F/TAF

Clinical trials using tenofovir alafenamide, coformulated into the E/C/F/TAF FDC include:

- **GS-US-292-0101**, a Phase 1 healthy volunteer study evaluating the relative bioavailability of EVG, FTC, TFV, and COBI administered as E/C/F/TAF STR relative to E/C/F/TDF or TAF (completed)

- **GS-US-292-0103**, a Phase 1 healthy volunteer study to evaluate the pharmacokinetics and relative bioavailability of the E/C/F/TAF STR relative to the individual components at GS-7340 doses of 10 mg (STR) or 25 mg Single Agent (SA) (completed)

- **GS-US-292-0110**, a Phase 1, randomized, open-label, single dose, three-treatment, three-period, six-sequence crossover study of the effect of food on the TAF component of the E/C/F/TAF STR (completed)

- **GS-US-292-0102**, a Phase 2 randomized, double-blinded study of the safety and efficacy of E/C/F/TAF STR versus E/C/F/TDF STR in HIV-1 infected, antiretroviral treatment-naive adults (completed)

- **GS-US-292-0106**, a Phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected antiretroviral treatment-naive adolescents (completed)

- **GS-US-292-0104** and **GS-US-292-0111**, Phase 3 randomized, double-blinded study of the safety and efficacy of E/C/F/TAF STR versus E/C/F/TDF STR in HIV-1 infected, antiretroviral treatment-naive adults (completed)

- **GS-US-292-0109**, a Phase 3 open-label study to evaluate switching from a TDF-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed, HIV-1 positive subjects (completed)

- **GS-US-292-0112**, a Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide single-tablet regimen in HIV-1 positive patients with mild to moderate renal impairment (completed)

- **GS-US-292-0117**, a Phase 3, two-part study to evaluate the efficacy of Tenofovir Alafenamide versus placebo added to a failing regimen followed by treatment with Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1 positive, antiretroviral treatment-experienced adults (ongoing)

- **GS-US-292-0119**, a Phase 3 open-label study to evaluate switching from optimized stable antiretroviral regimens containing darunavir to Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (E/C/F/TAF) single tablet regimen (STR) plus darunavir (DRV) in treatment experienced HIV-1 positive adults (ongoing)

Study GS-US-292-0101 is a Phase 1 study of 40 subjects evaluating the relative bioavailability of two different formulations of E/C/F/TAF STR, each with TAF dose of 25 mg or 40 mg, versus E/C/F/TDF STR or TAF 25 mg alone. Exposures of EVG, COBI, and FTC were comparable between E/C/F/TAF vs E/C/F/TDF regardless of formulation (monolayer or bi-layer). In contrast, TAF exposures were ~2.2-fold higher (and corresponding tenofovir exposures ~3-fold higher) when administered as E/C/F/TAF (25 mg) vs TAF SA 25 mg for both formulations of the E/C/F/TAF, likely mediated by inhibition of Pgp-mediated intestinal secretion of TAF by COBI.

Study GS-US-292-0102 is a completed, randomized, active-controlled Phase 2 study, compares E/C/F/TAF (10 mg) versus Stribild® (STB, E/C/F/TDF) in treatment-naïve, HIV-1 infected subjects. At Week 48, the E/C/F/TAF demonstrated potent antiviral efficacy (HIV-1 RNA < 50 copies/mL) similar to STB (88.4% [99/112] vs 87.9% [51/58] using the snapshot algorithm); in the E/C/F/TAF group, no patient had emergent resistance to 1 or more components of the E/C/F/TAF. Importantly, E/C/F/TAF demonstrated a potential benefit over E/C/F/TDF in terms of renal and bone safety: smaller median decreases in eGFR (mL/min) (at Week 48, E/C/F/TAF -5.5 vs E/C/F/TDF -10.0 [$P < 0.001$) and smaller median percentage decreases in BMD (at Week 48, spine E/C/F/TAF -1.00 vs E/C/F/TDF -3.37 [$P < 0.001$], hip -0.62 vs -2.39 [$P < 0.001$]).

Study GS-US-292-0103 is a completed Phase 1 healthy volunteer study which evaluated the PK and relative bioavailability of the E/C/F/TAF STR relative to the individual components at TAF doses of 10 (STR) or 25 mg SA. Results indicate that when dosed as the E/C/F/TAF 10 mg STR, TAF and TFV exposures were comparable to those observed with TAF 25 mg dosed alone. Exposures of EVG, COBI, and FTC were also comparable between the STR and individually dosed formulations.

In two controlled, double-blind phase 3 studies (GS-US-292-0104 and GS-US-292-0111), treatment-naive HIV-infected patients were recruited with an estimated creatinine clearance of 50 mL per min or higher from 178 outpatient centers in 16 countries. Patients were randomly assigned (1:1) to receive once-daily oral tablets containing 150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide (E/C/F/TAF) or 300 mg tenofovir disoproxil fumarate (E/C/F/TDF) with matching placebo. Randomization was done by a computer-generated allocation sequence (block size 4) and was stratified by HIV-1 RNA, CD4 count, and region (USA or ex-USA). Investigators, patients, study staff, and those assessing outcomes were masked to treatment group. All participants who received one dose of study drug were included in the primary intention-to-treat efficacy and safety analyses. The main outcomes were the proportion of patients with plasma HIV-1 RNA less than 50 copies per mL at Week 48 as defined by the US Food and Drug Administration (FDA) snapshot algorithm (pre-specified noninferiority margin of 12%) and pre-specified renal and bone endpoints at 48 weeks. There were 1733 patients who received treatment (866 given E/C/F/TAF and 867 given E/C/F/TDF). E/C/F/TAF was non-inferior to E/C/F/TDF, with 800 (92%) of 866 patients in the TAF group and 784 (90%) of 867 patients in the TDF group having plasma HIV-1 RNA less than 50 copies per mL (adjusted difference 2.0%, 95% CI -0.7 to 4.7). Patients given E/C/F/TAF had significantly smaller mean serum creatinine increases than those

given E/C/F/TDF (0.08 vs 0.12 mg/dL; $p < 0.0001$), significantly less proteinuria (median % change –3 vs 20; $p < 0.0001$), and a significantly smaller decrease in bone mineral density at spine (mean % change -1.30 vs -2.86; $p < 0.0001$) and hip (-0.66 vs -2.95; $p < 0.0001$) at 48 weeks. Interpretation through 48 weeks, more than 90% of patients given E/C/F/TAF or E/C/F/TDF had virological success. Renal and bone effects were significantly reduced in patients given E/C/F/TAF.

Study GS-US-292-0109 is a completed phase 3 study designed to evaluate the safety, efficacy, and tolerability of switching to E/C/F/TAF in HIV-infected patients who are virologically suppressed on regimens containing TDF. Patients meeting the inclusion criteria of an plasma HIV-1 RNA less than 50 copies per mL for ≥ 96 weeks on stable TDF-based regimen with estimated creatinine clearance > 50 mL/min were randomly assigned (2:1) to switch to E/C/F/TAF (n = 959) or maintain their TDF-based regimen (n = 477). The regimens at baseline were E/C/F/TDF (n = 459), EFV/FTC/TDF (n = 376), and RTV-boosted ATV + FTC/TDF (n = 601). The main outcomes were the proportion of patients with plasma HIV-1 RNA less than 50 copies per mL at Week 48 as defined by the US Food and Drug Administration (FDA) snapshot algorithm (pre-specified noninferiority margin of 12%) and pre-specified renal and bone endpoints at 48 weeks. In this study of 1436 virologically suppressed patients, switching to E/C/F/TAF was non-inferior and statistically superior to continuing TDF-based regimen, with 97% of E/C/F/TAF patients and 93% of patients maintaining an TDF-based regimen having plasma HIV-1 RNA less than 50 copies per mL at Week 48 (adjusted difference 4.1%, 95% CI: 1.6 to 6.7). Patients switching to E/C/F/TAF had significant improvements in serum creatinine ($p < 0.001$) and eGFR ($p < 0.001$) than those maintaining TDF-based regimen. There were no Grade 2-4 serum creatinine increases in patients that switched to E/C/F/TAF. The difference in bone mineral density changes from baseline to 48 weeks significantly favored the patients switching to E/C/F/TAF with increases observed compared maintaining an TDF-based regimens where there were decreases in mean % change in BMD (spine: -0.28 vs +1.79; $p < 0.001$ and hip: –0.26 vs + 1.37; $p < 0.001$). There were fewer discontinuations due to adverse events in the patients switching to E/C/F/TAF compared to continuing TDF-based regimen (0.9% vs 2.5%).

1.3. Rationale for This Study

Little data exist reporting on the safety and efficacy in switching from an abacavir/lamivudine (ABC/3TC) plus a third antiretroviral agent to a simple, once daily tablet of E/C/F/TAF FDC in adult patients who are virologically suppressed. This study seeks to enroll a large number of subjects to address this gap in the clinical literature. As part of the enrollment, up to 40 subjects who are 60 years or older will be enrolled. Since Study GS-US-292-0109 enrolled a relatively younger population, this study will also serve to provide data on the safety and efficacy of E/C/F/TAF FDC in an older population, an objective in keeping with the aging of the HIV-infected population.

1.4. Risk/Benefit Assessment for the Study

Potential risks of a patient's study involvement include switching to an unfamiliar regimen with potential loss of virologic control and/or new adverse events, the inconvenience of more frequent clinic visits and laboratory blood draws and the associated pain and discomfort of phlebotomy. Strategies to mitigate these risks include close monitoring of viral load, CD4+ T cell count and other lab values as well as monitoring of adverse events. Parameters for discontinuation of the study drug due to adverse events or lack of efficacy will be well-defined and closely followed.

Potential benefits may include the patient receiving a FDC antiretroviral E/C/F/TAF regimen that is more convenient leading to improved adherence, with potentially fewer adverse events than the current regimen.

Considering the above, the benefit-risk balance for this study is considered positive.

1.5. 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 to E/C/F/TAF FDC relative to continuing on a baseline regimen consisting of ABC/3TC plus a third antiretroviral agent in maintaining HIV-1 RNA < 50 copies/mL at Week 24 (using FDA snapshot algorithm) in virologically suppressed, HIV-1 infected adult subjects

The secondary objectives of this study are:

- To evaluate the proportion of subjects maintaining virological response (defined as HIV-1 RNA < 50 copies/mL, FDA snapshot analysis) at Weeks 12 and 48
- To evaluate changes from baseline in CD4+ cell counts at Weeks 24 and 48
- To evaluate the safety and tolerability of the two treatment groups over 24 and 48 weeks

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 as defined by the FDA snapshot algorithm

The secondary efficacy endpoints of this study are:

- Proportion of subjects with HIV-1 RNA <50 copies/mL at Weeks 12 and 48 as defined by the FDA snapshot algorithm
- The change from baseline in CD4+ cell counts at Weeks 24 and 48

3.2. Study Design

This protocol describes a randomized, open-label, multicenter study to evaluate the safety and efficacy of switching from ABC/3TC plus a third antiretroviral agent (as prescribed by the Investigator) to E/C/F/TAF FDC tablet compared to staying on their current regimen in 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.

3.3. Study Treatments

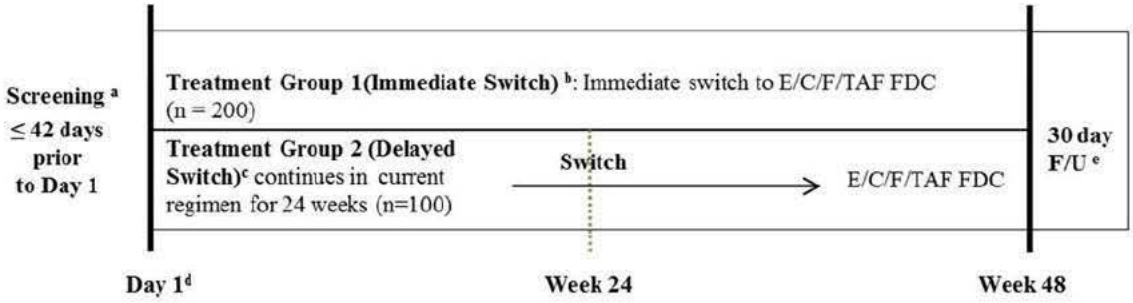
At Day 1, all subjects will be randomized (2:1) to one of two groups, either switch immediately from ABC/3TC to E/C/F/TAF FDC treatment (Treatment Group 1) or continuing on their existing regimen for 24 weeks followed by a delayed switch to E/C/F/TAF FDC (Treatment Group 2). Randomization will be stratified by age (< 60 years or ≥ 60 years).

- **Treatment Group 1:** Immediate switch from ABC/3TC plus a third antiretroviral agent to E/C/F/TAF FDC (n = 200)
- **Treatment Group 2:** Continue on the current regimen of ABC/3TC plus a third antiretroviral agent for 24 weeks followed by a delayed switch to E/C/F/TAF FDC (n = 100)

Allowed third antiretroviral agents include:

Antiretroviral Class	Agents
Boosted PI	ATV+COBI (or ATV/COBI FDC), DRV+COBI (or DRV/COBI FDC), DRV+RTV, LPV/r, ATV+RTV
NNRTI	EFV, ETR, NVP, RPV
INSTI	DTG, RAL

Figure 3-1. Study Schema



a Subjects will be screened within 42 days before the Day 1 visit to determine eligibility for participation in the study.
b Treatment Group 1: Immediate switch group. Switch from ABC/3TC plus a third antiretroviral agent to E/C/F/TAF FDC (n = approximately 200).
c Treatment Group 2: Delayed switch group. Continue on the current regimen of ABC/3TC plus a third antiretroviral agent for 24 weeks followed by a delayed switch to E/C/F/TAF FDC (n = approximately 100).
d Following the Day 1 visit, subjects will return for study visits at Weeks 4, 8, 12, 24, 36 and 48. Subjects randomized to treatment Group 2 will also return to the clinic at Week 28 and 32, four and eight weeks after switching to E/C/F/TAF FDC.
e Subjects who complete the study through Week 48 will be required to return to the clinic 30 days after the completion of the study drug for a 30-Day follow-up visit.

3.4. Duration of Treatment

The treatment duration is 48 weeks. After screening, eligible subjects will be randomized to Treatment Group 1 or 2 and treated for 48 weeks. Following the Screening and Day 1 visits, subjects will return for study visits at Weeks 4, 8, 12, 24, 36 and 48. Subjects randomized to Treatment Group 2 will also return for a visit at Weeks 28 and 32.

3.5. End of Study

End of study is defined as completion of the 48 weeks of treatment and the 30 Day Follow-Up visit.

3.6. Post Study Care

After a subject has completed/terminated the study participation, long-term care for the participant will remain the responsibility of their primary treating physician.

3.7. Source Data

Gilead will provide source document worksheets for all study visits.

3.8. Samples for Optional Exploratory Assessments

PPD

PPD

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 300 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 ABC/3TC plus a third antiretroviral (ARV) agent for ≥ 6 consecutive months prior to the screening visit. Subjects must be on their first or second ARV regimen. Refer to Table 4-1 for allowed third agents of the current regimen.

4) Documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 months preceding the screening visit (measured at least twice using the same assay).

   a) In the preceding 6 months prior to screening, one episode of "blip" (HIV-1 RNA > 50 and < 400 copies/mL) is acceptable, only if HIV-1 RNA is < 50 copies/mL immediately before and after the "blip".

   b) 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 (eg., LLOQ of 75 copies/mL).

5) Plasma HIV-1 RNA level < 50 copies/mL at screening visit

6) Documented historical genotype prior to starting initial ARV therapy (ART) showing no known resistance to TDF or FTC, including, but not limited to the presence of reverse transcriptase resistance mutants K65R, M184V/I, or thymidine analog-associated mutations (TAMs) (TAMs are: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R). If a historical genotype is not available, subject will have proviral genotype analysis for archived resistance at screening visit.

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

8) Adequate renal function:

   Estimated GFR ≥ 30 mL/min according to the Cockcroft-Gault formula ($eGFR_{CG}$) for creatinine clearance {2202}:

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

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

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

10) 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 × ULN)

11) Adequate hematologic function:

- Absolute neutrophil count ≥ 1,000/mm^3
- Platelets ≥ 50,000/mm^3
- Hemoglobin ≥ 8.5 g/dL

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

   a) Not pregnant confirmed by a negative serum pregnancy test which is required for female subjects (unless permanently sterile or greater than two years post-menopausal).

   b) Not nursing. Lactating females must agree to discontinue nursing before the study drug is administered.

   c) 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).

   d) Of childbearing potential (as defined in Appendix 5) and agrees to utilize the protocol specified method of contraception 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.

   e) 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 specified 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 90 days following the last study drug dose.

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

Antiretroviral Class	Agents
Boosted PI	ATV+COBI (or ATV/COBI FDC), DRV+COBI (or DRV/COBI FDC), DRV+RTV, LPV/r, ATV+RTV
NNRTI	EFV, ETR, NVP, RPV
INSTI	DTG, RAL

4.3. Exclusion Criteria

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

1) Previous use of any approved or experimental integrase strand transfer inhibitor (INSTI) (for any length of time) if the current regimen contains a PI/r

2) Subjects will have no evidence of previous virologic failure on a PI/r or INSTI-based regimen (with or without resistance to either class of ARV).

3) 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)

4) Hepatitis C virus that would require therapy during the study

5) Positive Hepatitis B surface antigen (HBsAg)

6) Subjects with clinical evidence of decompensated cirrhosis (ascites, encephalopathy, variceal bleeding)

7) Females who are breastfeeding

8) Positive serum pregnancy test

9) Have an implanted defibrillator or pacemaker

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

11) 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 1visit and must not be anticipated to require systemic therapy during the study.

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

13) 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

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

15) Known hypersensitivity to the study drug, the metabolites, or formulation excipients

16) Subjects receiving ongoing therapy with any of the medications in Table 4-2, including drugs not to be used due to the potential for interaction with 3TC, COBI, EVG, FTC, or TAF (for 3TC, COBI, EVG, or FTC refer to the individual agents' Prescribing Information; for TAF refer to the E/C/F/TAF FDC Investigator's Brochure); or subjects with any known allergies to the excipients of E/C/F/TAF FDC tablets.

Table 4-2. Disallowed Agents

Drug Class	Agents Disallowed*
Alpha Adrenergic Receptor Antagonists	Alfuzosin
Calcium Channel Blockers	Bepridil
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antihistamines	Astemizole, Terfenadine
Antimycobacterials	Rifampin, Rifapentine, Rifabutin
Ergot Derivatives	Ergotamine, Ergonovine Dihydroergotamine Methylergonovine Ergometrine
GI Motility Agents	Cisapride
Herbal/Natural Supplements	St. John's Wort, Echinacea
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin
Inhaled Beta Agonist	Salmeterol
Neuroleptics	Pimozide
Phosphodiesterase-5 Inhibitors	Sildenafil (for PAH)
Sedatives/Hypnotics	Orally administered Midazolam, Triazolam

* Administration of any of the above medications must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

Subjects will be randomized in a 2:1 ratio to Treatment Group 1 or Treatment Group 2. Randomization will be stratified by age (< 60 years or ≥ 60 years).

- **Treatment Group 1:** Immediate switch from ABC/3TC plus a third antiretroviral agent to E/C/F/TAF FDC (n = approximately 200)
- **Treatment Group 2:** Continue on the current regimen of ABC/3TC plus a third antiretroviral agent for 24 weeks followed by a delayed switch to fixed-dose regimen consisting of E/C/F/TAF FDC (n = approximately 100)

This is an open-label study.

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

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, it will not be reassigned to any other subject. The subject number assignment and randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed.

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

IWRS will assign open label study drug bottle numbers at each study visit for subjects in Treatment Group 1 and at Week 24 and onwards for subjects in Treatment Group 2. **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 for subjects in Treatment Group 1 and within 24 hours after the Week 24 visit for Treatment Group 2.

5.2. Description and Handling of E/C/F/TAF FDC

5.2.1. Formulation

E/C/F/TAF FDC tablets are capsule-shaped, film-coated green tablets and are debossed with "GSI" on one side of the tablet and "510" on the other side of the tablet. E/C/F/TAF FDC tablets contain 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF (as 11.2 mg of TAF fumarate).

In addition to the active ingredients, the tablets contain silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate as inactive ingredients and are film-coated with indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

5.2.2. Packaging and Labeling

E/C/F/TAF FDC tablets are packaged in white, high density polyethylene (HDPE) bottles. 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 with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

E/C/F/TAF FDC tablets should be stored at 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 drug should be stored in a securely locked area, accessible only to authorized site personnel.

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

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

5.3. Dosage and Administration of E/C/F/TAF FDC

E/C/F/TAF FDC tablets will be provided by Gilead Sciences.

Elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF) FDC will be administered orally, once daily with food at approximately the same time each day.

5.4. Prior and Concomitant Medications

The use of medications for the treatment of HIV, other than the study treatment (ie., E/C/F/TAF or ABC/3TC plus a third antiretroviral 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.

Table 5-1. Prior and Concomitant Medications

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
Acid Reducing Agents Antacids		Concentration of study drug may decrease with antacids. Subjects may not take antacids (eg, Tums, Mylanta); the ulcer medication sucralfate (Carafate); or vitamin or mineral supplements that contain calcium, iron or zinc for a minimum of 2 hours before and 2 hours after any dose of study drug.
Alpha Adrenergic Receptor Antagonists	Alfuzosin	
Analgesics		Tramadol, Propoxyphene: Concentrations may increase with study drug(s); clinical monitoring is recommended.
Antiarrhythmics		Amiodarone, Flecainide Quinidine, Propafenone, Systemic Lidocaine, Mexiletine, Disopyramide: Concentrations may increase with study drug(s) resulting in a potential for cardiac arrhythmias; clinical and ECG monitoring is recommended.
Calcium Channel Blockers	Bepridil	Felodipine, Nifedipine, Nicardipine, Verapamil, Diltiazem, Amlodipine: Concentrations may increase with study drug(s). Clinical and ECG monitoring of subjects is recommended
Digoxin		Digoxin: Concomitant use may result in increased levels; use with caution and with appropriate monitoring of serum digoxin levels. Digoxin therapy should be initiated at the lower dose, and the dose should be titrated to clinical response.
Antibacterials		Clarithromycin and Telithromycin: Concentrations may be altered with study drug(s); consider an alternative.
Anticoagulants		Warfarin: Concentrations may increase or decrease with study drug(s); appropriate INR (International Normalized Ratio) monitoring is recommended.
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	Ethosuximide, Divalproex, Lamotrigine: Concentrations may increase with study drug(s); clinical monitoring is recommended.

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
Antidepressants		Selective serotonin reuptake inhibitors (SSRIs): A dose reduction may be required for most drugs of this class with the exception of sertraline. Tricyclics: Concentrations may increase or decrease with study drug(s). Concentration monitoring is recommended to ensure adequate clinical response. Trazodone: Concomitant use with CYP3A inhibitors results in increased concentrations and adverse events; dose reduction should be considered.
Antifungals		Ketoconazole and Itraconazole: Concomitant use with study drug may result in an increase in concentrations. Daily dose of ketoconazole and itraconazole should be restricted to 200 mg. Subjects receiving ketoconazole or itraconazole should be monitored for adequate clinical response. Voriconazole: Concomitant use with study drug may result in an increase in concentrations. Clinical monitoring may be needed.
Antigout		Colchicine: Concentrations may increase with study drug(s). Dose reductions of colchicine may be required. Should not be coadministered in patients with renal or hepatic impairment. <u>Treatment of Gout Flare</u>: 0.6 mg (1 tablet) × 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course may be repeated no earlier than 3 days. <u>Prophylaxis of Gout Flares</u>: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. <u>Treatment of Familial Mediterranean Fever</u>: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antihistamines	Astemizole, Terfenadine	
Antimycobacterials	Rifampin, Rifapentine, Rifabutin	

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
β-Blockers		Metoprolol, Timolol: Clinical and ECG monitoring of subjects is recommended. A dose decrease may be needed.
Corticosteroids: Inhaled/Nasal		Concomitant use of inhaled fluticasone and study drug(s) may increase plasma concentrations of fluticasone. Use is not recommended unless the potential benefit to the subject outweighs the risks of corticosteroid side effects. Alternatives should be considered, particularly for long-term use.
Corticosteroids: Systemic		Systemic dexamethasone, a CYP3A inducer, may significantly decrease elvitegravir and cobicistat plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative corticosteroids should be considered. Use of Prednisone as a steroid burst (≤ 1 week of use) should be monitored appropriately.
Endothelin Receptor Antagonists		Bosentan: Coadministration may lead to decreased elvitegravir exposures and loss of therapeutic effect and development of resistance. Alternative endothelin receptor antagonists may be considered.
Ergot Derivatives	Ergotamine, Ergonovine Dihydroergotamine Methylergonovine Ergometrine	
GI Motility Agents	Cisapride	
Herbal/Natural Supplements	St. John's Wort, Echinacea	
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin	Atorvastatin: Concentrations may increase with study drug(s). Start with the lowest dose; gradual increase in dose may be tailored to clinical response. Careful monitoring for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.
Immunosuppressants		Cyclosporine, Rapamycin, Sirolimus, Tacrolimus: Concentrations may increase with study drug(s). Therapeutic monitoring should be considered.
Inhaled Beta Agonist	Salmeterol	
Neuroleptics	Pimozide	Perphenazine, Risperidone, Thioridazine: A dose decrease may be needed.

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
Opiates		Methadone: Methadone exposures are unaffected upon coadministration with elvitegravir and cobicistat. No dose adjustment of methadone is required upon coadministration with study drug(s). Meperidine (Pethidine): Dosage increase and long-term use are not recommended due to increased levels of metabolite normeperidine, which has analgesic and CNS stimulant (eg, seizures) activities. Buprenorphine: Concentrations of buprenorphine and norbuprenorphine are modestly increased and concentrations of naloxone are modestly decreased when coadministered with elvitegravir and cobicistat, with no effect on opioid pharmacodynimcs. The concentration changes are not considered clinically relevant and no dose adjustment of buprenorphine/naloxone is required upon coadministration with study drug(s).
Phosphodiesterase-5 Inhibitors	Sildenafil (for PAH)	<u>Pulmonary Arterial Hypertension</u>: Tadalafil: Caution should be exercised, including consideration of dose reduction, when coadministered for treatment of pulmonary arterial hypertension. <u>Erectile Dysfunction</u>: Sildenafil, Vardenafil, Tadalafil: It is recommended that a single dose of Sildenafil no more than 25 mg in 48 hours, Vardenafil no more than 2.5 mg in 72 hours, or Tadalafil no more than 10 mg in 72 hours be coadministered.
Sedatives/Hypnotics	Orally administered Midazolam, Triazolam	Buspirone, Clorazepate, Diazepam, Estazolam, Flurazepam, Zolpidem: A dose decrease may be needed for these drugs. Clinical monitoring is recommended.

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 Medical Monitor, the Investigator must notify Gilead 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. Accountability for Study Drug

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site. The Investigator (or designee) will be responsible for maintaining an accurate inventory (on study drug accountability records) of the dates and quantities of all study drug received, dispensed, and returned. Each dose of the study drug administered at the study center will be administered by qualified study center personnel. Each dose of the study drug administered at the study center will be administered by qualified study center personnel. The requirements of all applicable drug dispensing laws will apply to all doses of study drug dispensed by the Investigator (or designee).

The study drug 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.

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of study drug
- Record the date, subject number, subject initials, the study drug study drug bottle number dispensed
- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information.

5.5.1. Study Drug Return or Disposal

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

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

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 electronic Case Report Forms (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 Assessments

6.2.1. Screening Visit

Subjects will be screened within 42 days before Day 1 to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history, including history of HIV-1 disease-related events and prior medications within 30 days of the Screening visit
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), body weight, and height
- 12-lead ECG performed supine
- Urine collection for the following laboratory analyses:
  - Urinalysis and urine chemistry
- Blood sample collection for the following laboratory analyses:
  - Serum pregnancy test (females of childbearing potential only). If the test is positive, the subject will not be enrolled.
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, and sodium

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

— CD4+ cell count

— Plasma HIV-1 RNA (Taqman v2.0)

— Whole blood sample for proviral genotype analysis of archived resistance (if a historical genotype is not available)

— Hepatitis B virus surface antigen serology (HBsAg) and Hepatitis B core Antibody (HBcAb)

— Hepatitis C virus (HCV Ab) serology (reflex HCV RNA is performed in subjects with positive HCV Ab serology)

— Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance ($eGFR_{CG}$):

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

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

- Review of Concomitant Medications

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 42 days after screening for randomization into the study.

From the time of obtaining informed consent through the first administration of study drug, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events 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 evaluations before being dispensed the study drug. Initiation of treatment with the study drug must take place within 24 hours after this visit.

- Review of AEs and changes in concomitant medications

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

- Vital signs, including weight
- Urine collection for the following laboratory analyses:
  - Urinalysis and urine chemistry
  - Renal safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) retinol binding protein and beta-2 microglobulin
    - 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
  - 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.
  - Urine sample storage for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (glucose will be done as part of the fasting metabolic assessments)
  - Hematology profile
  - CD4+ cell count
  - Plasma HIV-1 RNA
  - Cystatin-C
  - $eGFR_{CG}$
  - 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.
  - Serum bone safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) parathyroid hormone (PTH) and serum 25-OH Vitamin D
    - 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.

— Platelet function and coagulation evaluations may include: Soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and D-dimer

— Inflammation evaluations, may include: cystatin-C, IL 6, hs CRP, sCD14, sCD163, sTNF-R1, and Lp-PLA2

— Plasma sample storage sample for safety and virology testing

— PPD

- Questionnaires: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.

  — Adherence (VAS)

  — HIV Treatment Satisfaction Questionnaire – Status version (HIVTSQs)

  — EQ-5D

  — Medical Outcomes Short Form 36 (SF-36)

  — Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-F)

6.3. Randomization

- Obtain subject number and randomize the subject via the IWRS.
- Treatment Group 1 subjects will be dispensed study drug as assigned via IWRS.
- Treatment Group 2 will continue with current ARV regimen until the Week 24 visit. Investigators must provide a prescription to the subjects in Treatment Group 2. Those subjects are responsible for obtaining their ARV treatment prior to or during the study visit.
- Subjects must initiate dosing of study drug within 24 hours after the Day 1 visit.
- Subjects should also be counseled regarding the importance of adherence and taking their study drug daily with food at approximately the same time each day.

6.4. Treatment Assessments

6.4.1. Treatment Visits (Weeks 4, 8, and 12)

The following evaluations are to be completed at the end of Weeks 4, 8, and 12, 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.

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

- Review of AEs and changes in concomitant medications
- Symptom-directed physical examination as needed
- Vital signs measurement, including weight
- Urine collection for the following laboratory analyses:
  - Urinalysis and urine chemistry
  - 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.
  - Renal safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) retinol binding protein and beta-2 microglobulin (**Weeks 4 and 12**)
    - 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.
  - Urine sample storage for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (glucose will be done as part of the fasting metabolic assessments at Week 12)
  - Hematology profile
  - CD4+ cell count
  - Plasma HIV-1 RNA
  - $eGFR_{CG}$

— 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) (**Week 12**)

  - 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.

— Serum bone safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) parathyroid hormone (PTH) and serum 25-OH Vitamin D including vitamin D and serum parathyroid hormone (PTH) (**Weeks 4 and 12**)

  - 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.

— Platelet and coagulation function evaluations may include: Soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and D-dimer (**Weeks 4 and 12**)

— Inflammation evaluations, may include: cystatin-C, IL 6, hs CRP, sCD14, sCD163, sTNF-R1, and Lp-PLA2 (**Weeks 4 and 12**)

— Plasma sample storage for safety and virology testing

— PPD

- Subjects who meet the criteria for virologic rebound should be managed according to Management of Virologic Failure (Section 6.11.1).
- Questionnaires: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.

  — Adherence VAS

  — HIV Treatment Satisfaction Change (HIVTSQc) (**Weeks 4 and 12**)

  — EQ-5D (**Week 4**)

  — SF-36 (**Week 4**)

  — FACIT-F (**Week 4**)

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

6.4.2. Treatment Assessments (Week 24)

The following evaluations are to be completed at the end of Week 24.

All study visits are to be scheduled relative to the Day 1 visit date. Study visits are to be completed within ± 6 days of the protocol-specified visit date based on the Day 1 visit.

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

Subjects randomized to Treatment Group 2 will be instructed to discontinue their previous ARV plus third agent regimen and will switch to the E/C/F/TAF FDC tablet and must initiate dosing of study drug within 24 hours after the Week 24 visit.

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs, including weight
- Urine collection for the following laboratory analyses:
  - Urinalysis and urine chemistry
  - Renal safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) retinol binding protein and beta-2 microglobulin
    - 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.
  - 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.
  - Urine sample storage for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (glucose will be done as part of the fasting metabolic assessments)
  - Hematology profile
  - CD4+ cell count
  - Plasma HIV-1 RNA

- $eGFR_{CG}$
- 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.
- Serum bone safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) parathyroid hormone (PTH) and serum 25-OH Vitamin D including vitamin D and serum parathyroid hormone (PTH)
  - 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.
- Platelet and coagulation function evaluations may include but not limited to: Soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and D-dimer
- Inflammation evaluations, may include but not limited to: Cystatin-C, IL 6, hs CRP, sCD14, sCD163, sTNF-R1, and Lp-PLA2
- Plasma sample storage for safety and virology testing
- PPD

- Subjects who meet the criteria for virologic rebound should be managed according to Management of Virologic Failure (Section 6.11.1).
- Questionnaires: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.
  - Adherence VAS
  - HIV Treatment Satisfaction Change (HIVTSQc)
  - EQ-5D
  - SF-36
  - FACIT-F
- Document study drug dispensation and accountability for all study drugs dispensed.

6.4.3. Treatment Assessments (Week 28 and 32) − Treatment Group 2 ONLY

The following evaluations are to be completed at the end of Week 28 and 32 for subjects randomized to Treatment Group 2, and who will be switched from their existing regimen to the E/C/F/TAF FDC at week 24.

Study visits are to be completed within ± 2 days of the protocol-specified visit date unless otherwise specified.

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

- Review of AEs and changes in concomitant medications
- Symptom-directed physical examination as needed
- Vital signs, including weight
- Urine collection for the following laboratory analyses:
  - Urinalysis and urine chemistry
  - Renal safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) retinol binding protein and beta-2 microglobulin (**Week 28**)
    - 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.
  - 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.
  - Urine sample storage for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile
  - Hematology profile
  - CD4+ cell count
  - Plasma HIV-1 RNA
  - $eGFR_{CG}$

- Serum bone safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) parathyroid hormone (PTH) and serum 25-OH Vitamin D including vitamin D and serum parathyroid hormone (PTH) (**Week 28**)
    - 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.
- Platelet and coagulation function evaluations may include but not limited to: Soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and D-dimer (**Week 28**)
- Inflammation evaluations, may include but not limited to: Cystatin-C, IL 6, hs CRP, sCD14, sCD163, sTNF-R1, and Lp-PLA2 (**Week 28**)
- Plasma sample storage for safety and virology testing
- PPD

- Subjects who meet the criteria for virologic rebound should be managed according to Management of Virologic Failure (Section 6.11.1).
- Questionnaires: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.
    - Adherence VAS
    - HIV Treatment Satisfaction Questionnaire − Change version (HIVTSQc) (**Week 28**)
    - EQ-5D (**Week 28**)
    - SF-36 (**Week 28**)
    - FACIT-F (**Week 28**)
- Document study drug dispensation and accountability.

6.4.4. Treatment Assessments (Weeks 36 and 48)

The following evaluations are to be completed at the end of Weeks 36 and 48, unless otherwise specified.

All study visits are to be scheduled relative to the Day 1 visit date. The Week 36 visit is to be completed within ± 6 days of the protocol-specified visit date based on the Day 1 visit. The visit window at Week 48 will be ± 6 weeks of the protocol-specified visit date, which coincides with the Week 48 statistical analysis window for HIV-1 RNA. Unless notified by Gilead, the Week 48 visit should be completed within ± 6 days of the visit date.

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

- Review of AEs and changes in concomitant medications
- Complete physical examination (**Week 48**) (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Symptom-directed physical examination, as needed (**Week 36**)
- Vital signs, including weight
- 12-lead ECG performed supine (**Week 48**)
- Urine collection for the following laboratory analyses:
  - Urinalysis and urine chemistry
  - Renal safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) retinol binding protein and beta-2 microglobulin (**Week 36 [Treatment Group 2 subjects only] and Week 48 [all subjects])**
    - 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.
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test.
  - Urine sample storage for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (glucose will be done as part of the fasting metabolic assessments at **Week 36 [Treatment Group 2 subjects only] and Week 48 [all subjects]**)
  - Hematology profile
  - CD4+ cell count
  - Plasma HIV-1 RNA
  - $eGFR_{CG}$

— 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) (**Week 36 [Treatment Group 2 subjects only] and Week 48 [all subjects]**)

  - 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.

— Serum bone safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) PTH and serum 25-OH Vitamin D (**Week 36 [Treatment Group 2 subjects only] and Week 48 [all subjects]**)

  - 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.

— Platelet and coagulation function evaluations may include but not limited to: sGPVI, P-selectin, soluble CD40 ligand, and D-dimer (**Week 36 [Treatment Group 2 subjects only] and Week 48 [all subjects]**)

— Inflammation evaluations, may include but not limited to: Cystatin-C, IL 6, hs CRP, sCD14, sCD163, sTNF-R1, and Lp-PLA2 (**Week 36 [Treatment Group 2 subjects only] and Week 48 [all subjects]**)

— Plasma sample storage for safety and virology testing (**Weeks 36 and 48**)

— PPD

- Subjects who meet the criteria for virologic rebound should be managed according to Section 6.11, Virologic Failure.
- HIV-1 geno/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 50 copies/mL (**Week 48**)
- Questionnaires: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.

  — Adherence VAS

  — HIV Treatment Satisfaction Questionnaire – Change version (HIVTSQc) (**Week 48**)

  — EQ-5D (**Week 48**)

  — SF-36 (**Week 48**)

  — FACIT-F (**Week 48**)

- Document study drug dispensation (**Week 36**) accountability (**Weeks 36 and 48**).

6.5. Post-treatment Assessments

6.5.1. Early Study Drug Discontinuation (ESDD) Visit

If the subject discontinues study drug prior to the Week 48 visit (Treatment Group 1 and Treatment Group 2 after delayed switch at Week 24) or their current regimen prior to the Week 24 visit (Treatment Group 2), the subject will be asked to return to the clinic within 72 hours of stopping study drugs for the ESDD visit. The subject will be asked to continue attending the scheduled study visits through Week 48.

At the ESDD 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 this visit:

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs, including weight
- 12-lead ECG
- Urine collection for the following laboratory analyses:
  - Urinalysis and urine chemistry
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test
  - Urine sample storage for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile
  - Hematology profile
  - CD4+ cell count
  - Plasma HIV-1 RNA
  - $eGFR_{CG}$

— Plasma storage sample for safety and virology testing

— PPD

- Questionnaire: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.

  — Adherence VAS

  — HIV Treatment Satisfaction Questionnaire − Change version (HIVTSQc)

- HIV-1 genotype/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 50 copies/mL

- Study drug accountability

6.5.2. 30-Day Follow-up Visit

Subjects who complete the study through Week 48 will be required to return to the clinic 30 days after the completion of study for the 30 Day Follow-Up visit.

Subjects who permanently discontinue study drug or their current regimen and refuse to continue study visits through Week 48 will be asked to return to the clinic after the completion of the ESDD visit for a 30 Day Follow-Up visit.

Subjects who permanently discontinue study drug or their current regimen and continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit will not be required to complete the 30-Day Follow-Up Visit.

A ± 6 days window may be used to schedule this visit. The following evaluations are to be completed at this visit:

- Review of AEs and changes in concomitant medications

- Symptom-directed physical examination

- Vital signs measurement, including weight

- Urine collection for the following laboratory analyses:

  — Urinalysis

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

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile
  - Hematology profile
  - Plasma HIV-1 RNA
  - CD4+ cell count

At the 30 Day Follow Up Visit, any evaluations showing abnormal results indicating that there is 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.

6.6. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study (see Section 6.7, Criteria for Discontinuation of Study Treatment) and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study.

6.7. Criteria for Discontinuation of Study Treatment

Study drug 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 degree. Following 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
- Lack of efficacy (virologic 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)

6.8. Other Evaluations

6.8.1. Blood and Urine Storage

From subjects who provide additional consent, a portion of the blood drawn at all visits (except screening, unscheduled or 30 Day Follow-Up) will be frozen and stored. A portion of the urine collected from all subjects at all visits (except screening, unscheduled, or 30 Day Follow-Up). These stored samples may be used by Gilead or our research partners to help answer questions about the study drug, HIV-1 infection and its associated conditions, or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without express consent of the study subjects. At the conclusion of this study, these samples may be retained in storage for Gilead for a period of up to 15 years.

6.8.2. Bone Safety and Inflammation

For all subjects, blood will be collected for selected evaluations of bone safety, including serum 25-OH Vitamin D and parathyroid hormone (PTH). Evaluations for inflammation may include: cystatin-C, IL 6, hs CRP, sCD14, sCD163, sTNF-R1, and Lp-PLA2. Collections will be made at Day 1, Weeks 4, 12, 24 and 48. For Treatment Arm 2 subjects collections will also be made at Weeks 28 and 36.

6.8.3. Markers of Platelet Function and Coagulation

For all subjects, blood will be collected for selected evaluations of platelet function and coagulation may include: soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand and D-dimer. Collections will be made at Day 1, Weeks 4, 12, 24 and 48. For Treatment Arm 2 subjects collections will also be made at Weeks 28 and 36.

6.8.4. Markers of Renal Tubular Function

For all subjects, urine will be collected for selected evaluations of renal tubular function may include retinol binding protein and beta-2 microglobulin. Collections will be made at Day 1, Weeks 4, 12, 24, and 48. For Treatment Arm 2 subjects collections will also be made at Weeks 28 and 36.

6.9. End of Study

End of study is defined as completion of the 48 weeks of treatment and the 30 Day Follow-Up visit.

6.10. Post Study Care

After a subject has completed/terminated their participation in the study, long-term care for the subject will remain the responsibility of their primary treating physician.

6.11. 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 two consecutive confirmed HIV-1 RNA test results of ≥ 50 copies/mL at a scheduled or unscheduled visit.

6.11.1. Management of Virologic Failure

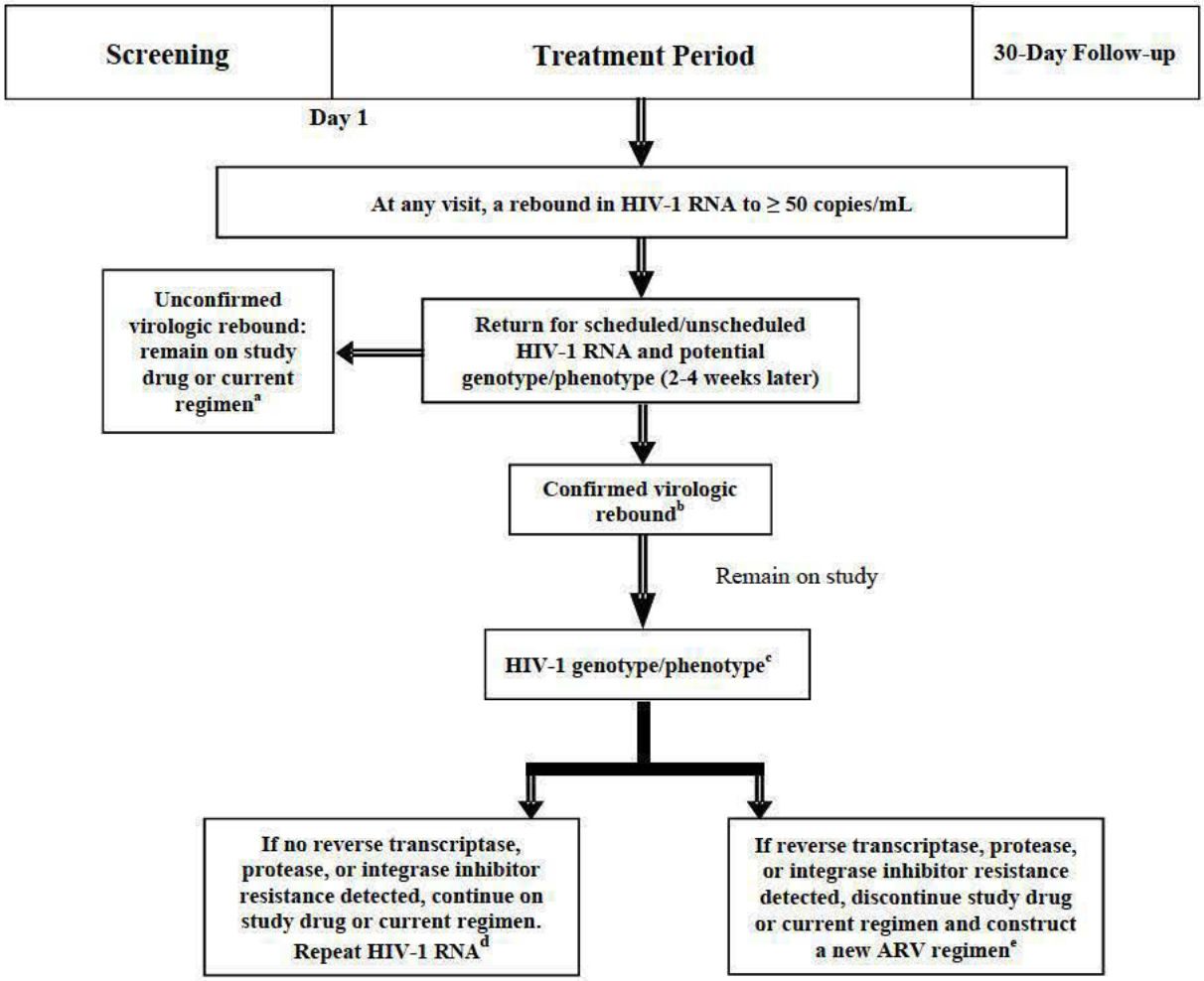
- If the viral load is ≥ 50 copies/mL, HIV-1 RNA should be repeated at a scheduled or unscheduled visit 2 to 4 weeks after the date of the original test with HIV-1 RNA ≥ 50 copies/mL.
- Upon confirmation of two consecutive results of HIV-1 RNA ≥ 50 copies/mL, potential causes of virologic failure should be documented. Assessments should include:
  - Adherence
  - Concomitant medication
  - Comorbidities (for example: active substance abuse, depression, other intercurrent illnesses)
- Investigators should discuss the management of all subjects with confirmed virologic failure with the Medical Monitor.
- If virologic failure is confirmed at the scheduled or unscheduled visit and HIV-1 RNA value is ≥ 50 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 or current regimen is documented, study drug or current regimen should be discontinued.
- If no resistance is detected from genotype/phenotype testing, subject may remain on study drug or current regimen and HIV-1 RNA should be repeated (2 to 4 weeks from the date of confirmed test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug or current regimen for each individual subject and document this assessment in the onsite medical record.

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

6.11.2. Resistance Analysis at Subjects Last Visit

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

Figure 6-1. Management of Virologic Failure



a If virologic rebound is not confirmed, the subject will remain on the study drug or their current regimen.
b If virologic rebound is confirmed, and the HIV-1 RNA is ≥ 50 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 or discontinue study drug or current regimen. 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/current regimen continuation/discontinuation options and discusses 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.

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 7.5.1)
- 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 CRF.

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 study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Appendix 3.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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 case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until 4 weeks after last administration of study drug 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 within 30 days of the last dose of study drug, regardless of causality, should also be reported.

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

All SAEs should be followed up until resolution if possible. If by the last day on study (including the off-study medication follow-up period) the SAE has not resolved, then the SAE will be followed up until the investigator and/or Gilead Sciences determine that the subject's condition is stable. However, Gilead Sciences may request that certain SAEs be followed until resolution.

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

7.3.3. 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 Sciences 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.

- 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 drug. 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 study drug 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 study drug.

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 drug and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and 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. 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:

Gilead Sciences DSPH:	Fax:	+1 (650) 522-5477
	E-mail:	safety_fc@gilead.com

Pregnancies of female partners of male study subjects are not collected for E/C/F/TAF protocols.

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 drug 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 Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

7.6. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3, as outlines below:

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

- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice.

- Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue study drug at the discretion of the Investigator.

7.6.2. Grade 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ Grade 2. When restarting study drug following resolution of the adverse event, the study drug should be restarted at full dose upon discussion with the Medical Monitor.

- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with study drug and is considered related to study drug, then study drug should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation but requires discussion with the Medical Monitor.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to study drug, study drug should be permanently discontinued and the 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.

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

7.6.4. 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 × 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 × 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 × 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.

7.6.5. 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 abacavir immediately and MUST NEVER be restarted. Restarting abacavir 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, abacavir 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}.

7.6.6. Management of Potential Nephrotoxicity

Estimated glomerular filtration rate, according to the Cockcroft-Gault ($eGFR_{CG}$) formula for creatinine clearance, will be followed post-baseline during the study. All subjects with estimated $eGFR_{CG} < 30$ mL/min must have serum creatinine measured again within 3 calendar days of receipt of results. At the time of this repeat serum creatinine assessment, Cystatin C will also be measured and the eGFR by CKD-EPI (cystatin C) will be calculated and compared with the baseline measurement. Any subjects who have an estimated $eGFR_{CG} < 30$ mL/min that also

experience > 20% reduction in eGFR by CKD-EPI (cystatin C) from baseline or who have other clinical and/or laboratory evidence of acute renal failure will be discussed with the Medical Monitor and may discontinue from study drugs. For subjects with $eGFR_{CG} < 30$ mL/min who are not discontinued based on toxicity management procedures above and considered to have stable renal function per Principal Investigator and Medical Monitor, it is not mandatory to repeat eGFR assessments within 3 days.

CKD-EPI (cystatin C) formula adjusted for age and sex:

$$eGFR\ (mL/min/1.73\ m^2) = 133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{1.328} \times 0.996^{Age} \quad [\times 0.932 \text{ if female}],$$

where Scys is serum cystatin C (mg/L), min (Scys/0.8,1) indicates the minimum of Scys/κ or 1, and max (Scys/0.8,1) indicates the maximum of Scys/κ or 1. All subjects with a change from baseline serum creatinine of ≥ 0.4 mg/dL must have serum creatinine repeated, with a concurrent urinalysis and urine chemistry, within two weeks of receipt of results. If a subject has a confirmed change from baseline serum creatinine of ≥ 0.4 mg/dL, the Medical Monitor should be notified and a consultation with a nephrologist should be obtained.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the efficacy of switching to E/C/F/TAF FDC relative to continuing on a baseline regimen consisting of ABC/3TC plus a third antiretroviral agent in maintaining HIV-1 RNA < 50 copies/mL at Week 24 (using FDA snapshot algorithm) in virologically suppressed, HIV-infected adult subjects

The secondary objectives of this study are:

- To evaluate the proportion of subjects maintaining virological response (defined as HIV-1 RNA <50 copies/mL, FDA snapshot analysis) at Weeks 12 and 48.
- To evaluate changes from baseline in CD4+ cell counts at Weeks 24 and 48.
- To evaluate the safety and tolerability of the two treatment groups over 24 and 48 weeks

8.1.2. Primary Endpoint

The primary endpoint is the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 as defined by the FDA snapshot algorithm.

8.1.3. Secondary Endpoint

Secondary efficacy endpoints are:

- Proportion of subjects with HIV-1 RNA <50 copies/mL at Weeks 12 and 48 as defined by the FDA snapshot algorithm
- The change from baseline in CD4+ cell counts at Weeks 24 and 48

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

Full Analysis Set (FAS)

The Full Analysis Set will include all the subjects who were randomized and received at least one dose of study drug. The FAS will exclude subjects with major protocol violations (e.g., not on the correctbaseline regimen regimen). Subjects will be grouped according to the treatment to which they were randomized. The FAS analysis set is the primary analysis set for the efficacy based analyses.

8.2.1.2. Safety

The primary analysis set for safety analyses is defined as all subjects that are randomized to the study and received at least one dose of study medication. Subjects will be grouped according to the treatment they actually received.

All data collected during treatment will be included in the safety summaries**.**

8.3. Demographic Data and Baseline Characteristics

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

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

Baseline data will include a summary of body weight, height, body mass index, risk factors for HIV-1 infection and enrollment distribution.

For categorical demographic and baseline characteristics, a Cochran-Mantel-Haenszel (CMH) test will be used to compare treatment groups. For continuous demographic and baseline characteristics, a Wilcoxon rank sum test will be used to compare treatment groups.

8.4. Efficacy Analysis

8.4.1. Primary Analysis

The null hypothesis is that the proportion of subjects maintaining HIV-1 RNA < 50 copies/mL (as defined by the FDA snapshot analysis) at Week 24 in the Treatment Group 1 (Immediate Switch) is at least 12% worse than the response rate in the Treatment Group 2 (Delayed Switch); the alternative hypothesis is that the response rate in Treatment Group 1 is less than 12% worse than that in Treatment Group 2.

The primary evaluation of non-inferiority at Week 24 will be done by constructing a two-sided exact 95% confidence interval for the difference in treatment group response rates (Treatment Group 1: E/C/F/TAF FDC minus Treatment Group 2: Continuing Baseline treatment regimen) using inverted two one-sided tests with the standardized statistic.

Once non-inferiority of Treatment Group 1 (E/C/F/TAF FDC treatment regimen) to Treatment Group 2 (Continuing Baseline 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 Treatment Group 1(E/C/F/TAF FDC) over Treatment Group 2 (continuing Baseline treatment regimen) will be established.

8.4.2. Secondary Analyses

The methods to assess proportion of HIV-1 RNA < 50 copies/mL at Weeks 12 and 48 using FDA snapshot analysis will be very similar to the primary endpoint analysis except the analysis window will differ and these analysis windows will be defined in the Statistical Analysis Plan.

The changes from baseline in CD4+ count at Weeks 24 and 48 will be summarized using descriptive statistics. The differences in changes from baseline between the two treatment groups and the associated 95% confidence intervals will be constructed using Analysis of Variance (ANOVA) model, including treatment group as fixed effect.

8.5. Safety Analysis

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

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

8.5.1. Extent of Exposure

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

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

8.5.2. 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.

Treatment-emergent adverse events are events that meet one of the following criteria up to 30 days after the permanent discontinuation of the study drug:

- Adverse events with onset dates on or after the first dose date of study drug and no later than 30 days after permanent discontinuation of study drug, or,
- Adverse events that result in permanent study drug 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 study drug, and effect on study drug dosing.

8.5.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the GSI Grading Scale for severity of Adverse Events and Laboratory Abnormalities (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 the date of last dose of study drug 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 drug or after the subject has been discontinued from treatment plus 30 days will be included in a data listing.

8.5.4. Other Safety Evaluations

Weight will be summarized by visit.

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

8.6. Biomarker Analysis

The renal, vascular and inflammatory markers will be summarized by treatment group and visit using descriptive statistics. The difference in change from baseline in these biomarkers between two treatment groups will be tested using Wilcoxon rank sum test.

8.7. Sample Size

With 200 subjects randomized to switch to the E/C/FTAF FDC at Day 1 and 100 subjects randomized to the delayed switch group at Week 24, the lower limit of the observed one sided 97.5% confidence interval will be expected to be greater than -0.120 (ie, non-inferiority margin of 12%) with > 90% power when the percentage of responders in both treatment groups for the primary endpoint is at least 90% at Week 24.

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, Washington, Seoul, 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, 1998, and 21 CFR, part 56, 1998.

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

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 a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions or in accordance with local regulations. 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's Brochure, this protocol, eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 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 study drug, 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. The eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. 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, 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. 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.

9.1.8. 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(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, 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.

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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, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Abacavir/Lamivudine (ABC/3TC) plus a Third Antiretroviral Agent to the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed HIV-1 Infected Adult Subjects

GS-US-292-1823, Original, 31 July 2015

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

Richard Haubrich
Name (Printed)
Author

PPD
Signature

8/10/15
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	Screening[a]	Day 1[b]	End of Week[c]								30 Day Follow-up[e]	ESDD[f]
			4	8	12	24[w]	28[d]	32[d]	36	48		
Informed Consent	X											
Medical History	X											
Concomitant Medications	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
Complete Physical Exam[g]	X	X				X				X		X
Symptom-Directed Physical Exam[h]			X	X	X		X	X	X		X	
12-Lead ECG (Performed Supine)	X									X		X
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X
Height	X											
Urinalysis and Urine Chemistry	X	X	X	X	X	X	X	X	X	X	X[u]	X
Urine Storage Sample		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
Serum Pregnancy Test[i]	X											
Chemistry Profile[j]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile[k]	X	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA[l]	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
Whole Blood Sample[m]	X											
HBV and HCV Serologies[n]	X											

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]								30 Day Follow-up[e]	ESDD[f]
			4	8	12	24[w]	28[d]	32[d]	36	48		
Metabolic Assessments[o]		X			X	X			X[d]	X		
Cystatin-C		X										
Estimated GFR_{CG}[p]	X	X	X	X	X	X	X	X	X	X		X
Plasma Storage Sample[q]		X	X	X	X	X	X	X	X	X		X
[redacted] PPD		X	X		X	X	X		X[d]	X		X
HIV-1 Genotype/Phenotype[r]										X		X
Evaluations of Bone & Renal Safety, Inflammation and Platelet and Coagulation Function[s]		X	X		X	X	X		X[d]	X		
Questionnaires: VAS, HIVTSQs, HIVTSQc, EQ-5D, SF-36, and FACIT-F[t]		X	X	X	X	X	X	X	X	X		X
Randomization		X										
Study Drug Dispensation and Accountability		X	X	X	X	X	X	X	X	X[v]		X

a Evaluations to be completed within 42 days prior to the 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. E/C/F/TAF FDC will be provided to subjects randomized to Treatment Group 1.
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. The Week 48 visit window is ± 6 weeks of the protocol specified date. Unless notified by Gilead, the Week 48 visit should be completed within ± 6 days of the visit date. For Treatment Group 2 subjects, the Weeks 28 and 32 visit windows are ± 2 days of the protocol specified date.
d Treatment Group 2 subjects only
e Only required for those subjects who permanently discontinue study drug or their current regimen and refuse continue study visits through Week 48. 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 Week 48 visit even if the subject discontinues study drug.
g Complete physical examination (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, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, and sodium. At visits in which metabolic assessments are to be performed, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.

k CBC with differential and platelet count

l 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 Day 1 results). HIV-1 genotype/phenotype resistance testing only conducted for subjects with confirmed virologic failure with HIV-1 RNA value ≥ 50 copies/mL. Subjects should be managed according to Figure 6-1.

m Whole blood sample for proviral genotype analysis of archived resistance (if a historical genotype report not available)

n Hepatitis B virus surface Antigen (HBsAg), Hepatitis B core antibody (HBcAb), and Hepatitis C virus (HBCAb) serologies (reflex HCV RNA is performed in subjects with positive HCVAb serology)

o Metabolic Assessments: 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.

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

q PPD

r HIV-1 genotype/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 50 copies/mL

s Blood for bone safety, parathyroid (PTH) and serum OH-25 vitamin D; Inflammation may include cystatin-C, IL-6, hs-CRP, sCD14, sCD163, sTNF-1R, and Lp-PLA2; Platelet and coagulation function may include soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and D-dimer will be collected. Urine for renal safety, including retinol binding protein, and beta-2-microglobulin, will be collected. Samples 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.

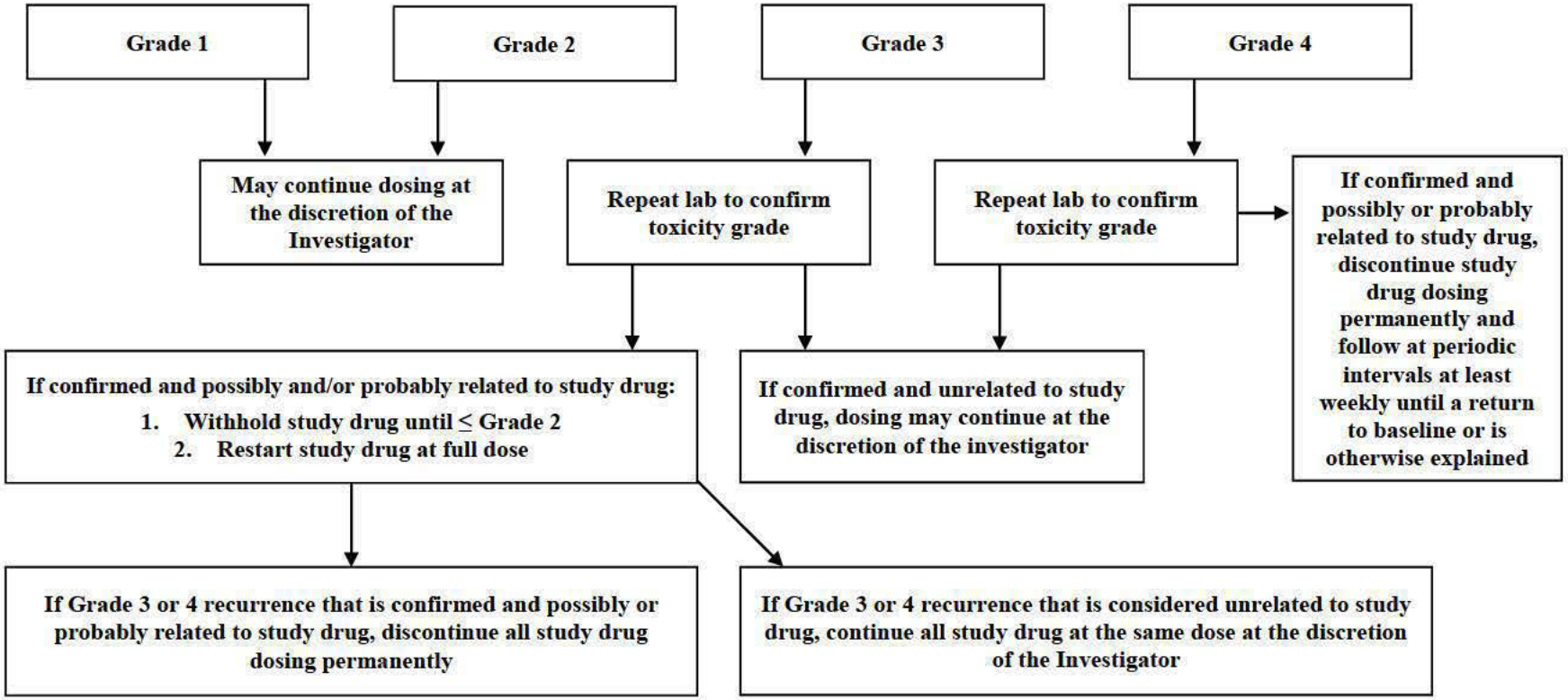
t EQ-5D, SF-36, and FACIT F will be administered at Day 1, Weeks 4, 24, 28 (Treatment Group 2 only) and 48. HIVTSQs will be administered on Day 1. HIVTSQc will be administered at Weeks 4, 12, 24, 28 (Treatment Group 2 only) 48 and ESDD. VAS will be administered at the following visits: Day 1 − Week 48 and ESDD.

u Urinalysis only

v Drug accountability only; study drug will not be dispensed at this visit.

w At Week 24, subjects randomized to Treatment Group 2 will discontinue their current regimen of ABC/3TC plus a third antiretroviral agent and will switch to E/C/F/TAF FDC; initiation of treatment with the study drug must take place within 24 hours after the Week 24 visit. E/C/F/TAF FDC will be provided to subjects.

Appendix 3. Management of Clinical and Laboratory Adverse Events



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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 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
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%

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 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	>ULN to 150 mEq/L >ULN 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 **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L 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 2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L 2.0 to < 2.5 mEq/L 2.0 t o <2.5 mmolL	< 2.0 mEq/L < 2.0 mmol/L < 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L >ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L > 6.0 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 > 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypouricemia **Adult and Pediatric ≥ 1 year** **Infant < 1 Year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN N/A	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L 1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L 0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L < 0.5 mg/dL < 27 µmol/L
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years** **Pediatric < 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN NA	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L 11.0 mEq/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L 8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L < 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
LDL (Fasting) Adult	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
LDL (Fasting) 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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

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

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

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatrics <16 years** **≥ 16 years**	- 3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < LLN g/dL 20 to < LLN g/L 2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L < 2.0 g/dL < 20 g/L	NA 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)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

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

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

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

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving 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 [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock

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 (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
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 (eg, status epilepticus), or difficult to control (eg, 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 (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

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

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

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years **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 (eg, 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 (eg, 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 (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

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

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic 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 (eg, septic shock)

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

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

1) Definitions

a) Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b) Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

The data of study drugs on pregnant women is limited or not available. There is no suspicion of human teratogenicity based on class effects or genotoxic potential. Relevant non clinical reproductive toxicity studies for human pregnancy do not indicate a strong suspicion of human teratogenicity/fetotoxicity. Data from clinical pharmacokinetic interaction studies of study drug have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception or that the effect on hormonal contraception is insignificant. Please refer to the latest version of the Investigator's Brochure for additional information.

b) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening prior to study enrollment. A pregnancy test will be performed at all study visits and the end of relevant system exposure. In the event of a delayed menstrual period (over one month between menstruations), a serum pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. Female subjects must agree to one of the following from Screening until 30 days following the end of relevant systemic exposure.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of one of the following methods of birth control listed below:

  — Intrauterine device (IUD) with a failure rate of < 1% per year

  — Tubal sterilization

  — Essure micro-insert system (provided confirmation of success 3 months after procedure)

  — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

  Or

- Consistent and correct use of one hormonal method and one barrier method:

  — Barrier methods

    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Male condom (with or without spermicide)

  — Hormonal methods (the hormonal contraceptive should contain at least 30 mcg of ethinyl estradiol)

    - Intrauterine hormone-releasing system (IUS) with a failure rate of < 1% per year
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

3) Contraception Requirements for Male Subjects

During the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

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 discontinue study drug immediately. Instructions for reporting pregnancy, and pregnancy outcome are outlined in Section 7.5.2.1.

Appendix 6. Definitions of HIV-1 Related Disease (CDC Guidelines) {35184}

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive†
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age > 1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy attributed to HIV§
- Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi sarcoma
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary†, disseminated, or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii (previously known as "Pneumocystis carinii") pneumonia
- Pneumonia, recurrent†

- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age > 1 month
- Wasting syndrome attributed to HIV[§]

* Only among children aged < 6 years
† Only among adults, adolescents, and children aged ≥ 6 years
§ Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references {7896}, {1238}.