CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Randomized, Open-Label Study to Evaluate Switching from a Tenofovir Disoproxil Fumarate (TDF) Containing Regimen to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed, HIV-1 Infected Subjects Aged ≥ 60 Years	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	111007	
EudraCT Number:	2015-002712-32	
Clinical Trials.gov Identifier:	NCT02616783	
Indication:	HIV-1 Infection	
Protocol ID:	GS-US-292-1826	
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Protocol Version/Date:	Original: Amendment 1:	22 July 2015 01 June 2016

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 3b, Randomized, Open-Label Study to Evaluate Switching from a Tenofovir Disoproxil Fumarate (TDF) Containing Regimen to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed, HIV-1 Infected Subjects Aged ≥ 60 Years
IND Number:	111,007
EudraCT Number:	2015-002712-32
Clinical Trials.gov Identifier:	NCT02616783
Study Centers Planned:	Approximately 30 centers in Europe
Objectives:	The primary objective of this study is: • To evaluate the safety of E/C/F/TAF FDC relative to unchanged current anti-retroviral therapy (ART) by assessing spine and hip bone mineral density (BMD) measured at Week 48 in virologically-suppressed, HIV-1 infected subjects aged ≥ 60 years The secondary objectives of this study are as follows: • To evaluate spine and hip BMD at Week 24 • To evaluate maintenance of HIV-1 RNA suppression < 50 copies/mL between regimens at Weeks 24 and 48 • To evaluate the safety and tolerability of the two treatment groups through Week 48
Study Design:	Randomized, open-label, multicenter, active-controlled study to evaluate switching from TDF and FTC or 3TC-containing 'backbone' regimen plus a third agent to E/C/F/TAF FDC in virologically-suppressed, HIV-1 infected subjects aged ≥ 60 years

	Subjects will be randomized in a 2:1 ratio to one of the following two treatment groups: • **Treatment Group 1:** FDC of elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF) once daily (n = 100) • **Treatment Group 2:** Remain on current TDF and FTC or 3TC-containing 'backbone' (maximum of 2 NRTIs) regimen plus continuing third agent (n = 50) Randomization will be stratified based on a bivariate cut-point of the screening spine and hip BMD T-score < −1.00 or ≥ −1.00. Subjects will be treated for 48 weeks in a randomized phase.
Number of Subjects Planned:	150
Target Population:	HIV-1 infected subjects ≥ 60 years old who are virologically-suppressed (HIV-1 RNA < 50 copies/mL) on a stable TDF and FTC or 3TC-containing 'backbone' (maximum of 2 NRTIs) regimen plus a third agent
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-1 infected adults who meet the following criteria: • Age ≥ 60 years • Currently receiving a TDF and FTC or 3TC-containing 'backbone' (maximum of 2 NRTIs) regimen plus a third agent continuously for ≥ 6 months preceding the screening visit. For subjects with 3 or more ART regimens, a regimen history must be provided for approval by the Sponsor. Allowed third agents include: LPV/r, ATV + RTV, ATV + COBI (or ATV/COBI FDC), DRV + RTV, DRV + COBI (or DRV/COBI FDC), FPV + RTV, SQV + RTV, EFV, RPV, NVP, ETR, RAL, EVG + COBI, 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

	• All documented historical plasma genotype(s) must not show resistance to TDF or FTC, including, but not limited to the presence of reverse transcriptase resistance mutations K65R, K70E, M184V/I or thymidine analog-associated mutations (TAMs) that include M41L, L210W, D67N, K70R, T215Y/F, K219Q/E/N/R. If historical plasma genotype prior to first ART is not available or subject has 3 or more ART regimens, subject will have proviral genotype analysis prior to Day 1 to confirm absence of archived resistance to TDF or FTC. • Adequate renal function defined as having an estimated glomerular filtration rate of ≥ 30 mL/min as calculated by Cockcroft-Gault ($eGFR_{CG}$) and are on ART that are appropriately dose adjusted for renal function per package insert • No 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
Study Procedures/ Frequency:	After screening, study visits will occur at Day 1, Weeks 4, 8, 12, 24, 36, and 48. Laboratory analyses (chemistry, hematology, 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. Blood and urine for selected evaluations of bone and renal safety, inflammation, and platelet and coagulation function will be collected at Day 1, Weeks 4, 12, 24, and 48. Dual-energy x-ray absorptiometry (DXA) scans will be performed at screening, Weeks 24 and 48. Scans will cover the spine and hip to measure changes in BMD.
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:	Current ART consisting of TDF and FTC or 3TC-containing 'backbone' (maximum of 2 NRTIs) regimen plus a third agent

Criteria for Evaluation:

Safety:	Primary Endpoints: • Percent change from Baseline to Week 48 in spine and hip BMD Secondary Endpoints: • Percent change from Baseline to Week 24 in spine and hip BMD
Efficacy:	Secondary Endpoints: • Proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the Food and Drug Administration (FDA) snapshot algorithm • Change from Baseline in CD4+ cell count at Weeks 24 and 48
Health Related Questionnaires:	Health related questionnaires will be administered, including the 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 (FACIT-F).
Statistical Methods:	The primary endpoints are the percentage change from baseline in spine and hip BMD at Week 48. The primary objective would be met if either one of these endpoints are statistically significant; the Type I error rate will be controlled using the fallback procedure. The primary endpoints: percent change from baseline in spine (and hip) BMD at Week 48 will be conducted using an ANOVA model, including treatment group and baseline spine (hip) BMD T-score in (< -1.00 vs ≥ -1.00) as a fixed effect in the model. Similar methods will be used at Week 24 for the BMD changes in hip and spine.
Sample Size:	In study GS-US-292-0109 (virologically-suppressed subjects switched from E/C/F/TDF to E/C/F/TAF) for subjects 55 or older, the mean percent change from baseline at Week 48 in hip BMD was +1.21 in the TAF group and −0.35 in the TDF group. The SD was 2.93 for the difference between the 2 groups resulting in an effect size of 0.53. The mean percent change from baseline at Week 48 in spine BMD was +1.71 in the TAF group and −1.32 in the TDF group. The SD was 4.24 for the difference between the 2 groups resulting in an effect size of 0.71. Given 150 subjects in the present study, there is at least 90% power to detect an effect size of 0.71 in spine BMD at Week 48 with a Type I error rate of $\alpha = 0.03$ and a power of 75% for hip BMD at Week 48 with

$\alpha = 0.02$ (in the situation that spine BMD is not statistically significantly different or 85% with $\alpha = 0.05$ in the situation that spine BMD is statistically significantly different) for an effect size of 0.53.

Descriptive statistics will summarize baseline characteristics, efficacy, and safety endpoints.

The secondary efficacy objective will assess maintenance of HIV-1 RNA suppression < 50 copies/mL by comparing the proportion of each group using the FDA snapshot algorithm.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ANOVA	analysis of variance
ARV	antiretroviral
AST	aspartate aminotransferase
ATR	Atripla®; EFV/FTC/TDF
ATV	atazanavir
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last measurable concentration
AUC_{tau}	area under the plasma concentration-time curve at the end of the dosing interval
AV	atrioventricular
BMD	bone mineral density
BUN	blood urea nitrogen
CBC	complete blood count
CK	creatine kinase
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CMH	Cochran-Mantel-Haenszel test
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
HCV	hepatitis C virus
HCVAb	hepatitis C virus serology
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HSP	hysterosalpingogram
IB	investigator's brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
INSTI	integrase strand transfer inhibitor

IMP	Investigational Medicinal Product
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
KS	Kaposi's sarcoma
LDH	lactate dehydrogenase
LLN	lower limit of the normal range
LLT	low-level term
LPV	lopinavir
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
Min	minute
mmHg	millimeters mercury
MVC	maraviroc
NNRTI	non-nucleoside reverse transcriptase inhibitor
N[t]RTI	nucleos(t)ide reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
P1NP	procollagen Type 1 N-terminal propeptide
PBMCs	peripheral blood mononuclear cells
PI	protease inhibitor
PK	pharmacokinetic
PT	preferred term
QD	once daily
RAL	raltegravir
RBC	Red blood cells
RNA	ribonucleic acid
RPV	rilpivirine
RTV, /r	ritonavir
SADR	serious adverse drug reaction
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure
STB	Stribild®, EVG/COBI/FTC/TDF (E/C/F/TDF) STR
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 C_{max}
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 {Campsmith et al 2010}, {World Health Organization (WHO) 2011}. 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 {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2012}.

The infection, if left untreated or suboptimally treated, 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 {Palella et al 1998}, {Mocroft et al 1998}, {Sterne et al 2005}.

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 {Department for Health and Human Services (DHHS) 2015}. 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 {Stone VE 2002}, {Chesney 2000}, {Department for Health and Human Services (DHHS) 2015}.

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 {Panel on Antiretroviral Guidelines for Adults and Adolescents 2012}. 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 a 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 is 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 {Sax et al 2015}.

1.2. Tenofovir Alafenamide (TAF, GS-7340)

1.2.1. General Information

Tenofovir alafenamide (GS-7340, TAF, or L-Alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]/phenoxyphosphinyl]-, 1-methylethyl ester) is a second generation oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP), a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the elongation of the viral DNA chain. In the development of TAF, three forms of the drug substance have been used in various studies: GS-7340, synonym for GS-7340 as the free base; GS-7340-02, synonym for TAF monofumarate (1:1); and GS-7340-03 as the hemifumarate (2:1). GS-7340-03, also known as TAF fumarate, is considered comparable based on physical/chemical properties to GS-7340-02 that has been used in previous studies and a number of ongoing studies. GS-7340-03 was also used in the Phase 2 study GS-US-292-0102 and several 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, refer to the current investigator's brochure for E/C/F/TAF.

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) {Robbins et al 1995} and nucleotide diphosphate kinase, which are highly active and ubiquitous. AK exists as multiple isozymes (AK1 to AK4), with the phosphorylation of TFV mediated most efficiently by AK2.

The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV. Metabolism of TAF was also studied in different human blood lymphocyte subpopulations, 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. 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-292-0102**, 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-292-0104** 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-292-0106**, 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-292-0109**, 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-292-0110**, 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-292-0112**, 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 was 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 was 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 was 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 E/C/F/TAF or 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 virologic success. Renal and bone effects were significantly reduced in patients given E/C/F/TAF.

1.3. Rationale for This Study

With the aging of the HIV-infected population such that half of the population is now over the age of 50 years, there is a need for efficacy and safety data in this population. This study seeks to address this gap by enrolling subjects 60 years or older in order to generate data on the efficacy and safety of E/C/F/TAF in this population.

1.4. Risk/Benefit Assessment

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 regimen that is more convenient leading to improved adherence, with potentially fewer adverse events than the current regimen, E/C/F/TAF may provide an alternative treatment for a patient population with fewer therapeutic options than the general HIV-1-infected population.

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 safety of E/C/F/TAF relative to unchanged current antiretroviral therapy (ART) by assessing spine and hip bone mineral density (BMD) measured at Week 48 in virologically-suppressed, HIV-1 infected subjects aged ≥ 60 years

The secondary objectives of this study are:

- To evaluate spine and hip BMD at Week 24
- To evaluate maintenance of HIV-1 RNA suppression < 50 copies/mL between regimens at Weeks 24 and 48
- To evaluate the safety and tolerability of the two treatment groups through Week 48

3. STUDY DESIGN

3.1. Endpoints

The primary endpoints of this study are:

- Percent change from Baseline to Week 48 in spine and hip BMD

The secondary endpoints of this study are:

- Percent change from Baseline to Week 24 in spine and hip BMD
- Proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the Food and Drug Administration (FDA) snapshot algorithm
- Change in CD4+ cell count from baseline at Weeks 24 and 48

3.2. Study Design

This protocol describes a randomized, open-label, multicenter, active-controlled study to evaluate switching from TDF and FTC or 3TC-containing 'backbone' (maximum of 2 NRTIs) regimen plus a third agent to E/C/F/TAF FDC in virologically-suppressed, HIV-1 infected subjects aged ≥ 60 years. Subjects with Hepatitis B co-infection will not be excluded.

3.3. Study Treatments

Subjects will be randomized in a 2:1 ratio to one of the following two treatment groups:

- **Treatment Group 1:** FDC of elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF) daily (n = 100)
- **Treatment Group 2:** Remain on current TDF and FTC or 3TC-containing 'backbone' (maximum of 2 NRTIs) regimen plus continuing third agent (n = 50)

Randomization will be stratified based on a bivariate cut-point of the screening spine and hip BMD T-score < −1.00 or ≥ −1.00.

3.4. Duration of Treatment

The randomized 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.

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 their participation in the study, long-term care for the subject 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

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 150 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 ≥ 60 years

3) Currently receiving a TDF and FTC or 3TC-containing 'backbone' (maximum 2 NRTIs) regimen plus a third agent for ≥ 6 consecutive months prior to screening visit. For subjects with 3 or more ART regimens, a regimen history must be provided for approval by the Sponsor. 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). 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".

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

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

6) Adequate renal function:

   Estimated glomerular filtration rate ≥ 30 mL/min according to the Cockcroft-Gault formula ($eGFR_{CG}$) and are on ARVs that are appropriately dose adjusted for renal function per package insert {Cockcroft et al 1976}:

   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)

7) All documented historical plasma genotype(s) must not show resistance to TDF or FTC, including, but not limited to the presence of reverse transcriptase resistance mutations K65R, K70E, M184V/I or thymidine analog-associated mutations (TAMs) that include M41L, L210W, D67N, K70R, T215Y/F, K219Q/E/N/R. If historical plasma genotype prior to first ART is not available or subject has 3 or more ART regimens, subject will have proviral genotype analysis prior to Day 1 to confirm absence of archived resistance to TDF or FTC.

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

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

10) Total bilirubin ≤ 1.5 mg/dL **and** normal direct bilirubin (subjects with documented Gilbert's syndrome or with atazanavir-associated hyperbilirubinemia may have total bilirubin up to 5 × ULN as long as direct bilirubin is normal)

11) Adequate hematologic function

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

12) Study performed DXA scan and T-score received prior to Day 1

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

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

6) Women 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 ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause.

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

7) Subjects receiving ongoing treatment for bone disease (eg, osteoporosis), including bisphosphonates, denosumab, and strontium ranelate

8) Have an implanted defibrillator or pacemaker

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

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

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

12) 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

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

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

15) 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 EVG, COBI, FTC, TAF, or 3TC (for EVG, COBI, FTC and 3TC 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 4-1. Allowable Antiretroviral Agents of Current Regimen

Antiretroviral Class	Agents
Boosted Protease Inhibitor (PI)	LPV/r, ATV + RTV, ATV + COBI (or ATV/COBI FDC), DRV + RTV, DRV + COBI (or DRV/COBI FDC), FPV + RTV, SQV + RTV
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	EFV, RPV, NVP, ETR
Integrase Strand Transfer Inhibitor (INSTI)	RAL, DTG, EVG + COBI

Table 4-2. Disallowed Agents

Drug Class	Agents Disallowed*
Alpha Adrenergic Receptor Antagonists	Alfuzosin
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antihistamines	Astemizole, Terfenadine
Antimycobacterials	Rifampin, Rifapentine, Rifabutin
Bisphosphonates	Any agent in this class (e.g. alendronate, ibandronate, etc)
Calcium Channel Blockers	Bepridil
Ergot Derivatives	Ergotamine, Ergonovine Dihydroergotamine Methylergonovine Ergometrine
GI Motility Agents	Cisapride
Herbal/Natural Supplements	St. John's Wort, Echinacea
Inhaled Beta Agonist	Salmeterol
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin
Neuroleptics	Pimozide
Phosphodiesterase-5 Inhibitors	Sildenafil (for PAH)
Sedatives/Hypnotics	Orally administered Midazolam, Triazolam
Other	probenecid, calcium > 500 mg/day, vitamin D3 or D2 > 800 IU/day, TNF-alpha antagonists (eg infliximab, etanercept, adlimumab, certolizumab, golimumab), teriparatide, denosumab, strontium ranelate

* 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. The randomization will be stratified based on a bivariate cut-point of the screening spine and hip BMD T-score < -1.00 or ≥ -1.00.

- **Treatment Group 1:** FDC of elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF) QD (n = 100)
- **Treatment Group 2:** Remain on current TDF and FTC or 3TC-containing 'backbone' (maximum of 2 NRTIs) regimen plus continuing third agent (n = 50)

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

IWRS will assign open-label study drug bottle numbers at each study visit for those subjects in Treatment Group 1. **All Day 1 visit tests and procedures must be completed prior to the administration of the first dose of study drug**. Initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit.

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 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 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 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.

- **Treatment Group 1:** FDC of Elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF) administered orally with food once daily at approximately the same time each day

5.4. Prior and Concomitant Medications

The use of medication for the treatment of HIV, other than the study treatment (ie, E/C/F/TAF or TDF and FTC or 3TC-containing ‘backbone’ regimen plus a third agent) is prohibited. Medications listed in the following table and use of herbal/natural supplements are excluded or should be used with caution while subjects are participating in the study due to potential drug-drug interactions.

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.
Inhaled Beta Agonist	Salmetrol	
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).

Drug Class	Agents Disallowed	Use Discouraged and to be Used with Caution
Antihistamines	Astemizole, Terfenadine	
Antimycobacterials	Rifampin, Rifapentine, Rifabutin	
β-Blockers		Metoprolol, Timolol: Clinical and ECG monitoring of subjects is recommended. A dose decrease may be needed.
Bisphosphonates	Any agent in this class (eg, alendronate, ibandronate, etc.)	
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: Concentrations may increase with study drug. Coadministration of salmeterol with study drug may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.

Drug Class	Agents Disallowed	Use Discouraged and to be Used with Caution
Neuroleptics	Pimozide	Perphenazine, Risperidone, Thioridazine: A dose decrease may be needed.
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.
Others	Probenecid, calcium > 500 mg/day, vitamin D3 or D2 > 800 IU/day, TNF-alpha antagonists (eg, infliximab, etanercept, adlimumab, certolizumab, golimumab), teriparatide, denosumab, strontium ranelate	

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. 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 drug 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 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. 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 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 the subject is eligible 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 randomization (Day 1 visit) 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: HIV-1 disease-related events, cigarette smoking (current or previous smoker), diabetes, family cardiovascular history, history of fractures (including fragility fractures), and prior medications within 30 days of screening visit.
- Obtain all available historical plasma genotype reports
- 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)
- Height and weight
- 12-lead ECG performed supine
- Urine collection for the following laboratory analyses:
  - — Urinalysis
  - — Urine chemistry

- Blood sample collection for the following laboratory analyses:

  — 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)

  — 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 glomerular filtration rate according to the Cockcroft-Gault formula ($eGFR_{CG}$)

  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)

- Whole blood sample for virology (if historical plasma genotype from prior to first ART is not available or subject has 3 or more ART regimens). For subjects with 3 or more ART regimens, the proviral genotype test result for archived resistance must be approved by the Sponsor.

- DXA Scan (spine and hip)

  — Once eligibility is confirmed the DXA scan will be performed on subjects prior to the Day 1 visit.

- 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 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 (including any recent fractures) and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement, 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 storage sample 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+
  - Plasma HIV-1 RNA
  - Cystatin-C
  - $eGFR_{CG}$
  - Testosterone level

- Metabolic assessments: Fasting (no food or drink, 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.
- 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 storage sample for safety and/or virology testing
- PPD [redacted]

- Questionnaires: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.
  - Visual Analog Scale (VAS)
  - HIV Treatment Satisfaction Status (HIVTSQs)
  - EQ-5D
  - Medical Outcome Study Short Form-36 (SF-36)
  - Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)

6.3. Randomization

- Obtain subject number and randomize the subject via the IWRS.
- Treatment Group 1 will be dispensed study drug as assigned via IWRS
- Treatment Group 2 will continue with current ARV regimen. Investigators must provide a prescription to the subjects in Treatment Group 2. Those subjects are responsible for obtaining their ART prior to or during the study visit

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (glucose will be done as part of the fasting metabolic assessments at Weeks 24 and 48)
  - Hematology profile
  - CD4+
  - Plasma HIV-1 RNA
  - $eGFR_{CG}$
  - Testosterone level
  - Metabolic assessments: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) (**Weeks 24 and 48**)
  - 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 (**Weeks 4, 12, 24, and 48**)
  - Platelet and coagulation function evaluations may include: soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and d-dimer (**Weeks 4, 12, 24, and 48**).
  - Inflammation evaluations may include: cystatin-C, IL 6, hs CRP, sCD14, sCD163, sTNF-R1, and Lp-PLA2 (**Weeks 4, 12, 24, and 48**).
  - Plasma storage sample for safety and/or virology testing
  - PPD [redacted]
- DXA scans for spine and hip may be performed ≤ 10 days before study visit (**Weeks 24 and 48**).
- 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 only**)

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (glucose will be done as part of the fasting metabolic assessments at Weeks 24 and 48)
  - Hematology profile
  - CD4+
  - Plasma HIV-1 RNA
  - $eGFR_{CG}$
  - Testosterone level
  - Metabolic assessments: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) (**Weeks 24 and 48**)
  - 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 (**Weeks 4, 12, 24, and 48**)
  - Platelet and coagulation function evaluations may include: soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and d-dimer (**Weeks 4, 12, 24, and 48**).
  - Inflammation evaluations may include: cystatin-C, IL 6, hs CRP, sCD14, sCD163, sTNF-R1, and Lp-PLA2 (**Weeks 4, 12, 24, and 48**).
  - Plasma storage sample for safety and/or virology testing
  - PPD [redacted]
- DXA scans for spine and hip may be performed ≤ 10 days before study visit (**Weeks 24 and 48**).
- 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 only**)

- Questionnaires: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.
  - Visual Analog Scale (VAS)
  - HIV Treatment Satisfaction Change (HIVTSQc) (**Weeks 4, 24, and 48**)
  - EQ-5D (**Weeks 24 and 48**)
  - SF-36 (**Weeks 24 and 48**)
  - FACIT-F (**Weeks 24 and 48**)
- Document study drug dispensation (**Weeks 4, 8, 12, 24, and 36**) and accountability.

6.5. Post-Treatment Assessments

6.5.1. Early Study Drug Discontinuation (ESDD) Visit

If a subject discontinues study drug or their current regimen prior to Week 48, the subject will be asked to return to the clinic within 72 hours 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 (including any recent fractures) and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement, including weight
- 12-lead ECG
- Urine collection for the following laboratory analyses:
  - Urinalysis and urine chemistry
  - Urine storage sample for possible additional clinical testing

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile
  - Hematology profile
  - CD4+
  - Plasma HIV-1 RNA
  - $eGFR_{CG}$
  - Plasma storage sample for safety and/or virology testing
  - PPD
- Questionnaire: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.
  - VAS
  - HIVTSQc
- HIV-1 geno/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 50 copies/mL
- 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.

Those subjects who permanently discontinue study drug or their current regimen and continue in the study through at least one subsequent visit after the ESDD visit will not be required to complete the 30 Day Follow-Up visit.

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

- Review of AEs (including any recent fractures) and changes in concomitant medications
- Symptom-directed physical examination

- Vital signs measurement, including weight
- Urine collection for the following laboratory analyses:
  - Urinalysis
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile
  - Hematology profile
  - CD4+
  - Plasma HIV-1 RNA

At the 30 Day Follow-Up 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.

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

PPD

s.

6.8.2. Bone Mineral Density Evaluations

DXA scans will cover the spine and hip to measure changes in BMD. A complete description of the procedures performed for DXA scans will be provided in the DXA Site Study Binder. Scans will occur at Screening, Week 24, and Week 48.

6.8.3. Bone Safety and Inflammation

For all subjects blood will be collected for bone safety, including serum 25-OH Vitamin D, 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.

6.8.4. Markers of Platelet Function and Coagulation

For all subjects, blood will be collected for selected evaluations of platelet function may include: soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and d-dimer at Day 1, Weeks 4, 12, 24, and 48.

6.8.5. 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 at Day 1, Weeks 4, 12, 24, and 48.

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.

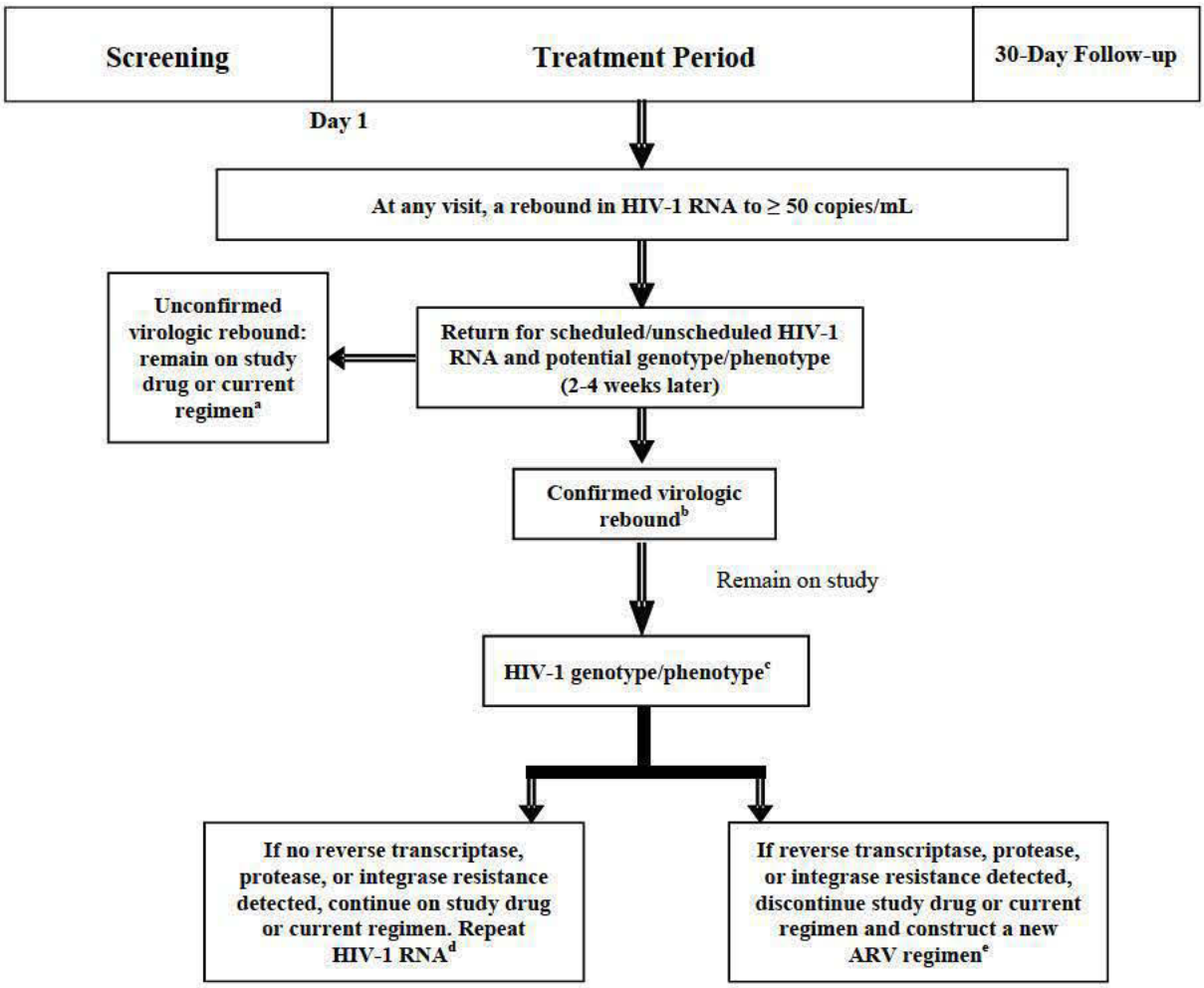
If no resistance is detected from genotype/phenotype testing, subject may remain on study drug or current regimen and a repeat HIV-1 RNA should be repeated (2-4 weeks from the date of confirmed test with viral load ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug 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 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 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 and 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 investigational medicinal product.

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

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

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

7.2.2. Assessment of Severity

Severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4). For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study drug, the following types of events should be reported on the eCRF:

- All SAEs and adverse events related to protocol-mandated procedures

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.

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 AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guidelines.

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 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, occupational exposure with an AE, AEs in infants that occur while breastfeeding, 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 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 associated with an adverse event is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the study drug associated with an adverse event, which is any untoward medical occurrence in a study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the study drug.

Occupational exposure with an AE is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

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 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 do 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 outlined 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 study drug discontinuation, unless such a delay is not consistent with good medical practice.

- Any questions regarding toxicity management should be directed to the Gilead 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 Bone Evaluation

As there is uncertainty surrounding the clinical significance and management of decreases in bone mineral density for HIV-1 infected patients, Gilead recommends that any subject who has a DXA scan that demonstrates a decrease from baseline of > 5% in the spine region or > 7% in the hip region be followed per local medical practice at the discretion of the Investigator.

7.6.5. Management of 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 $eGFR_{CG}$ 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:

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

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.

7.6.6. On-Treatment ALT Flare and Post-Treatment Exacerbation of Hepatitis Management

On-Treatment ALT Flare is defined as:

- Confirmed (within 3 days of receipt of initial laboratory results) serum ALT > 2 × Day 1 value and >10 × ULN, with or without associated symptoms

7.6.6.1. Management of ALT Flare in Subjects Receiving Study Medication

If laboratory results indicate elevation of ALT > 2 × Day 1 value and > 10 × ULN, the following is recommended:

- Schedule the subject to return to the clinic as soon as possible (ideally within 3 days after initial laboratory results were drawn). During the visit, a clinical assessment of the subject will be performed. The assessment should include a physical examination and evaluation of the subject's mental status.

- If the ALT elevation is confirmed, request the central clinical laboratory to conduct reflex testing for HBV DNA, HBV serology (HBsAg and HBsAb), HDV, HAV IgM, and HCV serology.

Check the following laboratory parameters: serum ALT and AST, total bilirubin, INR, and serum albumin. Based on the results of the confirmatory tests, the following treatment modifications are recommended:

Elevated Liver Enzymes, Normal or Stable Relative to Day 1 Liver Function Tests

If ALT levels are elevated (i.e., > 2 × Day 1 and > 10 × ULN) with normal or stable total bilirubin and INR relative to Day 1, the subject may remain on study medication and should be monitored weekly as long as ALT levels return to normal or Day 1 level. During monitoring, if the ALT values remain persistently elevated, the Investigator should discuss with the Gilead Medical Monitor whether the study drug should be discontinued.

For subjects with bridging fibrosis or cirrhosis, study drug discontinuation with treatment-free follow-up is to be avoided due to the potential risk of exacerbation of hepatitis in the setting of low hepatic reserve which could lead to decompensation. Subjects with bridging fibrosis or cirrhosis should be placed on an HIV regimen containing commercially available HBV therapy if study drug is discontinued.

Elevated Liver Enzymes, Elevated Liver Function Tests

If ALT values are elevated (i.e., > 2 × Day 1 and > 10 × ULN), and total bilirubin is confirmed to be 2 × Day 1 value, and INR is 0.5 above Day 1, provided both are > ULN, the investigator should consider discontinuing study medication (upon discussion with the Gilead Medical Monitor, unless the safety of the patient is of immediate concern). The subject should be monitored weekly as long as ALT, total bilirubin, and INR values remain elevated or above Day 1 values.

During monitoring, if the ALT values and the liver function tests remain persistently elevated, the Investigator should discuss with the Gilead Medical Monitor whether the study drug should be discontinued.

For subjects with bridging fibrosis or cirrhosis, study drug discontinuation with treatment-free follow-up is to be avoided due to the potential risk of exacerbation of hepatitis in the setting of low hepatic reserve which could lead to decompensation. Subjects with bridging fibrosis or cirrhosis should be placed on an HIV regimen containing commercially available HBV therapy if study drug is discontinued.

7.6.6.2. Management of Exacerbation of Hepatitis in Subjects Who Have Discontinued Study Medication

If laboratory results indicate (1) an ALT elevation > 2 × Day 1 and > 10 × ULN alone OR associated with (2) abnormal laboratory parameters suggestive of worsening hepatic function (total bilirubin 2 × Day 1, INR 0.5 above Day 1, provided both are > ULN) and the subject is on no post-study therapy for HBV, the following is recommended:

- Schedule the subject to return to the clinic as soon as possible (ideally no later than 3 days after the initial laboratory values were drawn). During the visit, perform a clinical assessment of the subject.

- Check the following laboratory parameters: serum ALT and AST, bilirubin, INR, and albumin.

- If the ALT elevation is confirmed, request the clinical laboratory to conduct reflex testing for HBV DNA, HBV serology (HBsAg and HBsAb), HDV, HAV IgM and HCV. If HBV DNA is increasing, the investigator should consider immediate initiation of approved therapy.

- The subject should be followed until laboratory parameters (ALT, total bilirubin, INR) return to normal or Day 1 up to a maximum of 6 months after the initial occurrence of the event.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the safety of E/C/F/TAF FDC relative to unchanged current anti-retroviral therapy (ART) by assessing spine and hip bone mineral density (BMD) measured at Week 48 in virologically-suppressed, HIV-1 infected subjects aged ≥ 60 years

The secondary objectives of this study are as follows:

- To evaluate spine and hip BMD at Week 24
- To evaluate maintenance of HIV-1 RNA suppression between regimens at Weeks 24 and 48
- To evaluate the safety and tolerability of the two treatment groups through Week 48

8.1.2. Primary Endpoint

The primary endpoints are:

- Percent change from Baseline to Week 48 in spine and hip BMD

8.1.3. Secondary Endpoint

Secondary endpoints are:

- Percent change from baseline to Week 24 in spine and hip BMD
- Proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the Food and Drug Administration (FDA) snapshot algorithm
- Change from baseline in CD4+ cell count 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 [eg, not on the correct standard baseline regimen (SBR) 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 HIV RNA based analyses.

8.2.1.2. Safety

8.2.1.2.1. Safety Analysis Set

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

8.2.1.2.2. Spine DXA Analysis Set

The primary analysis set for primary endpoint of spine BMD is defined as all subjects who are randomized and received at least one dose of study drug, and had non-missing spine BMD value at baseline visit and at least one post baseline visit. Subjects will be grouped according to the treatment they actually received.

8.2.1.2.3. Hip DXA Analysis Set

Hip DXA Analysis Set for primary endpoint of hip BMD, is defined as all subjects who are randomized and received at least one dose of study drug, and had non-missing hip BMD value at baseline visit and at least one post baseline visit. Subjects will be grouped according to the treatment they actually received.

8.3. Data Handling Conventions

In general, baseline value is defined as the last value measured on or prior to Day 1 of the randomized phase of the study.

If the primary endpoints of spine and hip BMD measurements at Week 48 are missing, then it will be imputed with Week 24 measurement or the last post-baseline measurement available, ie, last observed carried forward (LOCF).

8.4. Demographic Data and Baseline Characteristics

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

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

Baseline data 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.

8.5. Primary Analysis

8.5.1. Spine BMD

The primary endpoints are percentage change from baseline in spine and hip BMD at Week 48. If the primary endpoint of spine BMD is statistically significant ($\alpha = 0.03$), then the hip BMD will be tested using the fallback procedure, see details in Section 8.6.

For the hip BMD analysis, the analysis methods will be similar to those used for spine BMD analysis outlined below.

The hypotheses of interest for the spine BMD will be:

$$\mathbf{H_0}: d = 0$$
$$\mathbf{H_a}: d \neq 0$$

where d is the mean percentage change from baseline in spine BMD at Week 48 for E/C/F/TAF group (Treatment Group 1) minus that for SBR group (Treatment Group 2).

The primary analysis of the percentage change from baseline in spine BMD at Week 48 will be conducted using an ANOVA model, including treatment group and baseline spine BMD T-score (< -1.00 vs ≥ -1.00) as a fixed effect in the model.

8.5.2. Secondary Analyses

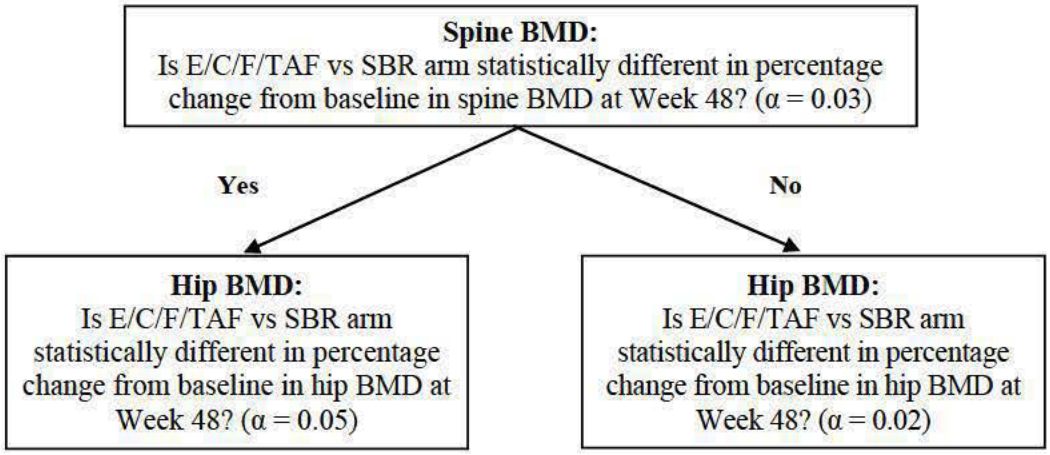
Similar methods will be used at Week 24 for the BMD percentage changes in spine or hip as the primary analysis.

The secondary efficacy endpoint is the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 and Week 48 as defined by the FDA snapshot algorithm using the full analysis set (FAS).

The two-sided exact 95% confidence interval for the difference in treatment group response rates (E/C/F/TAF minus SBR) will be constructed using inverted two one-sided tests with the standardized statistic.

8.6. Statistical Testing Procedure

To control for Type I error in the assessment of 2 primary efficacy endpoints, the hypothesis testing will be performed using the fallback procedure {Centers for Disease Control and Prevention (CDC) 2008}.



8.7. Safety Analysis

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

All safety data collected on or after the date that 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 period and the period post last dose plus 30 days will be included in data listings.

8.7.1. 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.

8.7.2. 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 adverse events that meet one of the following criteria:

- 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.

8.7.3. 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 (ie, at least a Grade 1) will be considered treatment emergent. The maximum toxicity grade will be summarized by laboratory parameter.

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

8.7.4. 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.

8.8. Sample Size

In Study GS-US-292-0109 (virologically-suppressed subjects switched from E/C/F/TDF to E/C/F/TAF) for subjects 55 or older, the mean percent change from baseline at Week 48 in hip BMD was +1.21 in the TAF group and −0.35 in the TDF group. The SD was 2.93 for the difference between the 2 groups resulting in an effect size of 0.53. The mean percent change from baseline at Week 48 in spine BMD was +1.71 in the TAF group and −1.32 in the TDF group. The SD was 4.24 for the difference between the 2 groups resulting in an effect size of 0.71. Given 150 subjects in the present study, there is at least 90% power to detect an effect size of 0.71 in spine BMD at Week 48 with a Type I error rate of $\alpha = 0.03$ and a power of 75% for hip BMD at Week 48 with $\alpha = 0.02$ (in the situation that spine BMD is not statistically significantly different) or 85% with $\alpha = 0.05$ in the situation that spine BMD is statistically significantly different) for an effect size of 0.53.

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. 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 IEC. The Investigator will not begin any study subject activities until approval from the 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 IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial 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 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 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, 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, 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, IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae, 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 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. Electronic Case Report Forms (eCRFs)

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 her/his login 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 (eg, 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. Study Drug Accountability and Return

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

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The Investigator must submit all protocol modifications to the IEC in accordance with local requirements and receive documented 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 agencies. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical 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) 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 Switching from a Tenofovir Disoproxil Fumarate (TDF) Containing Regimen to Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed, HIV-1 Infected Subjects Aged ≥ 60 Years

GS-US-292-1826, Amendment 1, 01 June 2016

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

Richard Haubrich, MD

Medical Monitor

PPD

Signature

1 June 2016

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

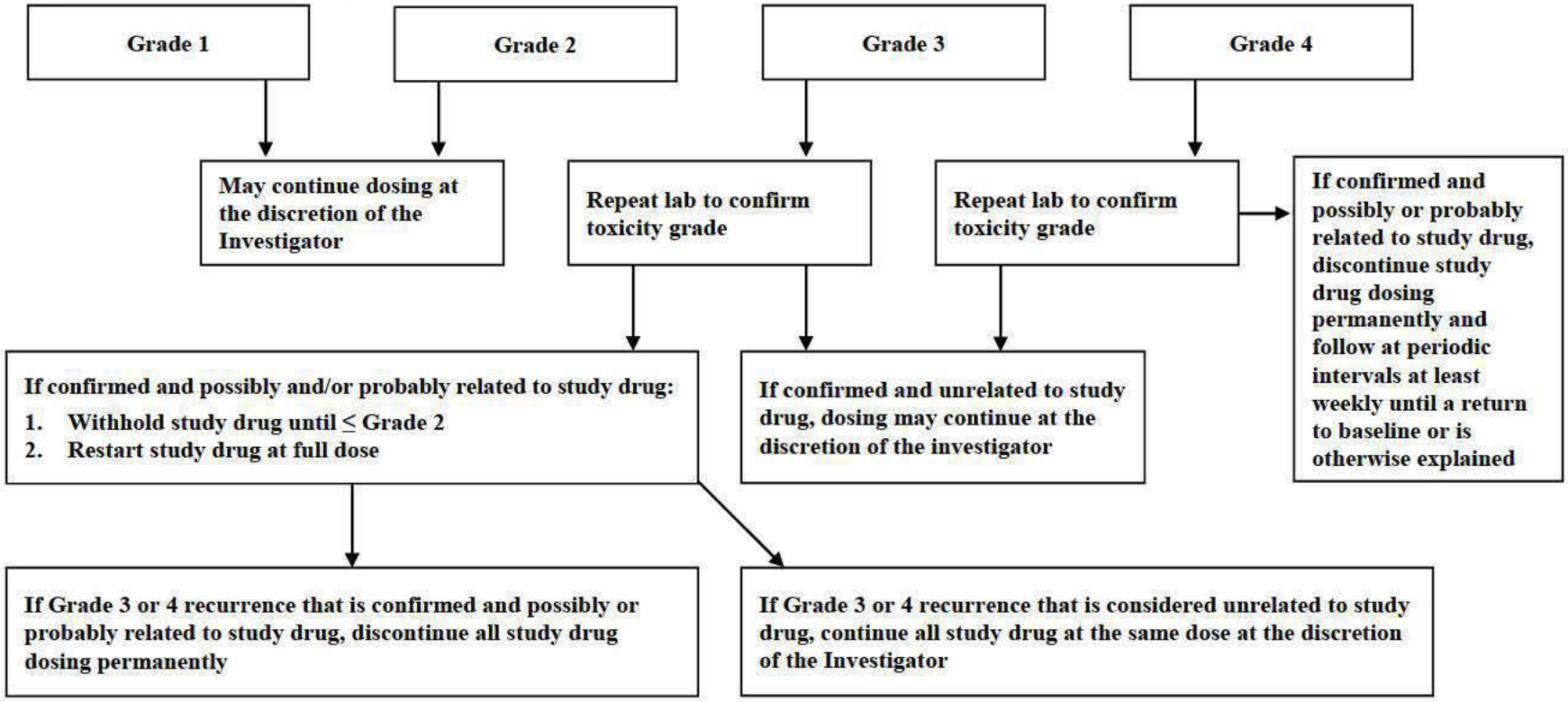
Appendix 2. Study Procedures Table

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						30 Day Follow-up	Early Study Drug Discontinuation[d] (ESDD)
			4	8	12	24	36	48		
Informed Consent	X									
Medical History	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam[e]	X	X				X		X		X
Symptom-Directed Physical Exam[f]			X	X	X		X		X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X
Height	X									
12-lead ECG	X							X		X
Urinalysis and Urine Chemistry	X	X	X	X	X	X	X	X	X[s]	X
Urine Storage Sample		X	X	X	X	X	X	X		X
Chemistry Profile[g]	X	X	X	X	X	X	X	X	X	X
Hematology Profile[h]	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA[i]	X	X	X	X	X	X	X	X	X	X
HBV and HCV Serologies[j]	X									
Cystatin-C		X								
Estimated GFR_{CG}[k]	X	X	X	X	X	X	X	X		X
Whole Blood Sample[l]	X									
Testosterone Level		X	X	X	X	X	X	X		
Metabolic Assessments[m]		X				X		X		
Evaluations of Bone & Renal Safety, Inflammation, and Platelet & Coagulation Function[n]		X	X		X	X		X		
Plasma Storage Sample[o]		X	X	X	X	X	X	X		X
PPD										
DXA Scan[p]	X					X		X		
Questionnaires: VAS,HIVTSQs, HIVTSQc, EQ-5D, SF-36, and FACIT-F[q]		X	X	X	X	X	X	X		X

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						30 Day Follow-up	Early Study Drug Discontinuation[d] (ESDD)
			4	8	12	24	36	48		
HIV-1 Genotype/Phenotype[r]								X		X
Randomization		X								
Study Drug Dispensation and Accountability		X	X	X	X	X	X	X[t]		X[t]

a Evaluations to be completed within 42 days prior to Day 1 visit.
b Subjects will be dispensed study drug at 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 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 for Weeks 24 & 36. The Week 48 visit window is ± 6 weeks of the visit date. Unless notified by Gilead, the Week 48 visit should be completed within ± 6 days of the visit date.
d Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the Week 48 visit even as the subject discontinues study drug.
e Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator).
f Symptom-directed physical examination as needed at Weeks 4, 8, 12, and 36
g 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 Day 1, Weeks 24 and 48 analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.
h CBC with differential and platelet count
i 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.
j 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)
k Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
l Whole blood sample for virology analysis (if historical plasma genotype report prior to first ART is not available or subject has 3 or more ART regimens)
m 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.
n 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 for bone and renal safety 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.
o Plasma storage sample for safety and/or virology (Day 1, Weeks 4-48, and ESDD). PPD
p DXA scan to be performed on all eligible subjects prior to study randomization. Screening BMD results via T-score must be available to randomize subject at Day 1. At Weeks 24 and 48, DXA may be performed ≤ 10 days before study visit.
q VAS will be administered at Day 1, Week 4-48, and ESDD. EQ-5D, SF-36, and FACIT-F will be administered at Day 1, Weeks 24 and 48. HIVTSQs will be administered on Day 1. HIVTSQc will be administered at Weeks 4, 24, 48 and ESDD.
r HIV-1 genotype/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 50 copies/mL
s Urinalysis only
t Drug accountability only; study drug will not be dispensed at this visit.

Appendix 3. Management of Clinical and Laboratory Adverse Events



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

Antiviral Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days** HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L 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	7.5 to < 8.5 g/dL 75 to < 85 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	6.5 to < 7.5 g/dL 65 to < 75 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	< 6.5 g/dL < 65 g/L < 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months**[#]	1000 to 1300/mm^3 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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 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
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	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 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
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 (e.g., 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 (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

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 (e.g., 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, e.g., Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g., Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

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

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

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

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

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weak-ness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

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

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

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

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

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

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (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 (e.g., 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 ≥ 54 years of age with cessation of previously occurring menses for ≥ 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 fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements

Females of childbearing potential are excluded from participation in the study; therefore no form of birth control will be required of any female subject enrolled into the study. During the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

3) 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.

4) 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 90 days or 12 weeks 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. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the Investigator. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.5.2.1.

Appendix 6. AIDS-Defining Conditions (CDC Guidelines) {Selik et al 2014}

- 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 {Centers for Disease Control and Prevention 1992}, {Centers for Disease Control and Prevention 1994},.