CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of E/C/F/TAF Fixed Dose Combination (FDC) in HIV-1 Infected Subjects on Chronic Hemodialysis	
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PROTOCOL SYNOPSIS

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Study Title:	A Phase 3b Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of E/C/F/TAF Fixed Dose Combination (FDC) in HIV-1 Infected Subjects on Chronic Hemodialysis
IND Number:	111,007
EudraCT Number:	2015-002713-30
Clinical Trials.gov Identifier:	Not available
Study Centers Planned:	Approximately 50 study sites in North America and Europe
Objectives:	The primary objective of this study is as follows: • To evaluate the safety and tolerability of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF; E/C/F/TAF) fixed dose combination (FDC) in HIV-1 infected adults with end stage renal disease (ESRD) on chronic hemodialysis (HD) at Week 48 The secondary objectives of this study are as follows: • To evaluate the proportion of subjects achieving virologic response (defined as HIV-1 RNA < 50 copies/mL, Snapshot analysis) at Weeks 24 and 48 • To evaluate plasma pharmacokinetics (PK) of EVG, COBI, FTC, TAF and TFV in HIV-1 infected patients with ESRD on HD
Study Design:	Open-label, multicenter, single-arm study to assess the safety, tolerability, pharmacokinetics, and efficacy of E/C/F/TAF FDC dosed once daily in HIV-infected adult subjects with ESRD on chronic HD. All subjects will switch from their current antiretroviral (ARV) regimen to E/C/F/TAF on Day 1. The treatment duration will be 48 weeks.
Number of Subjects Planned:	Approximately 50 subjects with ESRD on chronic HD will be enrolled.

Target Population:	HIV-1 infected adults (≥ 18 years) with ESRD on chronic HD for ≥ 6 months prior to screening, and HIV-1 RNA < 50 copies/mL on a stable antiretroviral (ARV) regimen for ≥ 6 consecutive months prior to screening.
Duration of Treatment:	Subjects will be treated for 48 weeks.
Diagnosis and Main Eligibility Criteria:	HIV-1-infected adults who meet the following criteria: • No documented history of HIV-1 resistance to EVG, FTC, 3TC or TFV • Currently receiving a stable antiretroviral regimen for ≥ 6 consecutive months prior to screening • Plasma HIV-1 RNA < 50 copies/mL for at least 6 months preceding the screening visit • CD4+ T cell count of ≥ 200 cells/μL • ESRD with eGFR < 15 mL/min by Cockcroft-Gault, on chronic HD for ≥ 6 months prior to screening • Hepatitis C (HCV) infection allowed • Hepatitis B (HBV) infection not allowed
Study Procedures/ Frequency:	Following Screening, eligible subjects will be required to return for study visits at Day 1, Weeks 2, 4, 8, 12, 24, 36 and 48. After the Week 48 visit, subjects will stop study drug and complete a 30-Day Follow-up visit to complete their participation in the study. For all subjects, HBV and HCV serologies will be analyzed at Screening. Adverse events, concomitant medications, complete or symptom-directed physical examinations, laboratory analyses (hematology and chemistry), fasting lipids and glucose, HIV-1 RNA, CD4+ T cell count and estimated GFR will be performed at the Screening, Day 1, and all subsequent study visits. Pre-dose blood draw for plasma and PBMC samples will be collected from all subjects at Week 4 or Week 12, which must be the day of hemodialysis. All subjects who provide consent will be eligible to participate in the pharmacokinetic sub-study (target n = 15).
Test Product, Dose, and Mode of Administration:	FDC of elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg administered orally once daily with food until the next hemodialysis. On the day of hemodialysis, study drug should be administered should occur after completion of hemodialysis.

Reference Therapy, Dose, and Mode of Administration:	N/A

Criteria for Evaluation:

Safety:	Safety evaluations will include reporting of adverse events, clinical laboratory tests, physical examinations, and vital signs. An Independent Data Monitoring Committee (IDMC) will be convened after the first 25 subjects enrolled in the study complete Week 12 of the study.
Efficacy:	Virologic response will be determined using the percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 24 and 48 (snapshot analysis).
Pharmacokinetics:	At Week 4 or Week 12, on the day of hemodialysis, pre-dose (within 30 minutes prior to study drug administration) blood draws for plasma and PBMC samples will be collected from all subjects. Study drug administration will be observed. Plasma concentrations of EVG, COBI, FTC, TAF and TFV and intracellular concentrations of TFV-DP may be explored. <u>Pharmacokinetic (PK) Sub-study</u> All subjects who provide consent will be eligible to participate in the PK sub-study (target n = 15). For the PK sub-study, intense blood sampling will be conducted at or between Week 2 or Week 4 study visits, on a day prior to the day of hemodialysis and when the subject has administered three doses of E/C/F/TAF between two hemodialysis sessions. The PK of EVG, COBI, FTC, TAF and TFV will be evaluated. Study drug administration will be observed in-clinic at the sub-study visit.
Health Related Questionnaires:	SF-36, VAS (visual analogues scale), HIV-TSQ (HIV Treatment Satisfaction Questionnaire) and Health Utilization Questionnaire will be administered per the information provided in the study procedures section of this protocol.

Statistical Methods:	The primary endpoint will be the incidence of treatment-emergent Grade 3 or higher adverse events at Week 48. The proportions of subjects with virologic response (HIV-1 RNA < 50 copies/mL, snapshot analysis) and the associated 95% confidence intervals at Weeks 24 and 48, respectively will be constructed.

Concentrations and PK parameters of EVG, COBI, FTC, TAF and TFV for the sub-study, and intracellular PBMC concentrations of TFV-DP will be summarized using descriptive statistics [N, mean, standard deviation, percent coefficient of variation (%CV), median, minimum, and maximum].

A sample size of approximately 50 subjects is based on practical consideration and is considered to be sufficient to evaluate the primary objective of this study. The grade 3 or higher AE rate in Study GS-US-292-0112 in subjects that had mild to moderate renal impairment was 8.8% at Week 48 for the E/C/F/TAF arm. Therefore, with 50 subjects, and an assumed rate of Grade 3 or higher AEs being 10%, this study would provide 95% confidence for the primary endpoint to be (1.7%, 18.3%) assuming normal approximation to binomial proportions.

A sample size of at least 15 subjects is considered for estimating the PK parameters in the sub-study for practical reasons.

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
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
bsAP	serum bone specific alkaline phosphatase
BMD	bone mineral density
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{min}	minimum plasma concentration
CNS	central nervous system
C_{tau}	the observed drug concentration at the end of the dosing interval
CPK	creatine phosphokinase
CRF	case report form(s)
CRO	contract (or clinical) research organization
CYP	cytochrome P450
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
E/C/F/TAF	elvitegravir (EVG) 150 mg / cobicistat (COBI) 150 mg / emtricitabine (FTC) 200 mg / tenofovir alafenamide (TAF) 10 mg fixed dose combination
ESRD	End stage renal disease
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination
FS	failure to suppress
FTC	emtricitabine
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
HD	hemodialysis
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HIV-TSQ	HIV Treatment Satisfaction Questionnaire
HIV-TSQs	HIV Treatment Satisfaction Questionnaire Status
HIV-TSQc	HIV Treatment Satisfaction Questionnaire Change
HMG-CoA	5-hydroxy-3-methylglutaryl-coenzyme A
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
DMC	Data Monitoring Committee
IND	Investigational New Drug (Application)
INSTI	integrase strand transfer inhibitor
IRB	institutional review board
IWRS	interactive web response system
LDH	lactate dehydrogenase
LLN	lower limit of the normal range
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MH	Mantel-Haenszel
Min	minute
mmHg	millimeters mercury
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OC	osteocalcin
P1NP	procollagen Type 1 N-terminal propeptide
PBMCs	peripheral blood mononuclear cells
PI	protease inhibitor
PK	pharmacokinetic
PT	preferred term
PTH	parathyroid hormone
QD	once daily

RNA	ribonucleic acid
SAE	serious adverse event
SVR	suboptimal virologic response
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	tenofovir alafenamide (GS-7340)
TAF fumarate	tenofovir alafenamide fumarate (GS-7340-03)
TDF	tenofovir disoproxil fumarate
TFV-DP	tenofovir diphosphate (TFVpp)
T_{max}	the time (observed time point) of C_{max}
ULN	upper limit of the normal range
US	United States
VR	virologic rebound

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus-1 infection is a life-threatening and serious disease of major public health significance, with approximately 34 million people infected with HIV worldwide {19661}. The goals of highly active antiretroviral therapy (HAART) for HIV-1 infection are to delay disease progression and prolong survival by achieving maximal and durable suppression of HIV-1 replication. Prompt antiretroviral therapy (ART) initiation after diagnosis is based on growing evidence that untreated HIV infection or uncontrolled viremia is associated with development of non- acquired immune deficiency syndrome (AIDS)-defining diseases, including cardiovascular disease (CVD), kidney disease, liver disease, neurologic complications, and malignancies. The success of ART has shifted clinical attention towards regimens that optimize long-term adherence, tolerability and safety. Adherence to ART is required to prevent development of drug resistance and subsequent loss of virologic suppression, and adherence to ART is improved by reducing pill burden and dosing frequency {4266}, {4256}. Once-daily, single tablet regimens are associated with high adherence, better clinical outcomes, including fewer hospitalizations, improved patient satisfaction, and excellent virologic outcomes {7034}, {7035}, {7036}, {16557}, {16560}.

Despite current therapy that effectively suppresses viremia, HIV disease remains a serious condition due to non-AIDS associated comorbidities. As treatment guidelines recommend early treatment of HIV-1 infection, there is a need for regimens offering enhanced product safety and tolerability, effectiveness, and convenience for long-term treatment.

Though antiretroviral drugs have led to dramatic improvements in survival and disease progression, complications such as kidney, liver, and cardiac disease have become increasingly important causes of morbidity and mortality for HIV patients taking effective therapy {19947}, {19948}, {22552}. Recent data has shown that even with treatment, HIV patients experience more age-related co-morbidities, such as renal and bone disease, which manifest earlier than their age-matched HIV-uninfected peers {19946}. Moreover, the prevalence and incidence of chronic kidney disease (CKD) and end stage renal disease (ESRD) in the US are expected to rise as the prevalence of HIV infection continues to rise {22553}. Worldwide, prevalence may be even greater; one cross-sectional study in the East African Republic of Burundi reported 46% of HIV-positive adults fulfilled criteria for CKD {22551}.

Patients with HIV are at risk for acute and chronic kidney disease from a wide spectrum of etiologies, including HIV-associated nephropathy, immune complex kidney disease, thrombotic microangiopathy, and kidney disease associated with comorbidities such as diabetes, hypertension, hepatitis B and hepatitis C coinfections, as well as medications associated with nephrotoxicity. Clearly, new therapies that improve on the current standard of care are needed, so that life-long antiviral therapy is more effective, more tolerable, and safer for patients. Since the majority of currently available nucleos(t)ide backbones are prescribed as fixed dose combinations, HIV-positive patients with chronic kidney disease have particularly limited therapeutic options.

The availability of a single tablet regimen composed of potent agents with improved tolerability and long-term safety, that does not require dose adjustment at eGFR < 50 mL/min, would represent an important therapeutic innovation in this special patient population, providing more convenient dosing and potentially improving patient adherence.

Tenofovir alafenamide (TAF) has a unique metabolism that provides enhanced lymphatic delivery of tenofovir, resulting in higher intracellular levels of the active phosphorylated metabolite, tenofovir-diphosphate (TFV-DP), and lower circulating levels of TFV {7415}, {13119}, {22029}. The distinct metabolism of TAF offers an improved clinical profile compared with TDF, which is associated with nephrotoxicity and decreased bone mineral density {21762}, {22031}. Compared with TDF, TAF is characterized by lower systemic exposures and higher intracellular levels of TFV. Additionally, TFV exposures achieved with TAF in subjects with severe renal impairment are comparable to those with normal renal functions receiving TDF 300 mg, indicating that TAF can be administered to HIV-1 infected patients with renal impairment without dose modification.

1.2. Tenofovir Alafenamide (TAF, GS-7340)

1.2.1. General Information

Tenofovir alafenamide (GS-7340, TAF, or L-alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]/phenoxyphosphinyl]-, 1-methylethyl ester) is an prodrug of TFV, a nucleotide analog that inhibits HIV-1 reverse transcription. TFV is metabolized intracellularly to the active metabolite, TFV-DP, a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the elongation of the viral deoxyribonucleic acid (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) molar ratio of TAF to fumaric acid; and GS-7340-03 as the hemifumarate (2:1) molar ratio of TAF to fumaric acid. 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. GS-7340-03 and GS-7340-02 exist as the free base, TAF (GS-7340), in blood and biological fluids.

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. Primary Pharmacodynamics

Tenofovir alafenamide is metabolized to TFV, a nucleotide analog (ie, a nucleoside monophosphate analog) which is not dependent on an intracellular nucleoside kinase activity for the first step in the conversion to the active metabolite, TFV-DP. The cellular enzymes responsible for TFV metabolism to the active diphosphorylated form are adenylate kinase (AK) {4887} 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, natural killer (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

Single doses of TAF 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).

1.2.3. Nonclinical Pharmacokinetics

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

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

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

- Peak TFV plasma concentrations occurred following TAF absorption, with TFV T_{max} values between 0.25 to 1.7 hours in rats, dogs, and monkeys.

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

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

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

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

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

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

1.2.4. Nonclinical Toxicology

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

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

- In chronic studies in rats, bone (atrophy of metaphyseal cancellous bone) and kidneys (karyomegaly) were the primary target organs after 26 weeks of treatment with TAF 100 mg/kg/day; however, effects were not seen at lower doses. Tenofovir alafenamide also appeared to increase biochemical markers of bone turnover and decrease serum 1,25-dihydroxy- and 25-hydroxyvitamin D3 at doses of 25 mg/kg/day and above.

- In chronic studies in dogs after 9 months of treatment at doses up to TAF 18/12 mg/kg/day (the high dose was reduced from 18 to 12 mg/kg/day due to the occurrence of death, severe clinical signs and reduced body weight), the primary target organs were kidney (slight to moderate renal tubular degeneration and karyomegaly) and bone (decreased bone mineral density [BMD] in metaphyseal cancellous bone).

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

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

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

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

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

Emtricitabine and TAF have been combined with the integrase inhibitor EVG and its pharmacoenhancer COBI in the E/C/F/TAF FDC, which has been designed to be a complete treatment regimen for HIV-1 infection and is being evaluated in a broad clinical development program. The details of the key clinical studies are provided below:

- **GS-US-292-0102**, a randomized, double-blinded controlled Phase 2 study in which E/C/F/TAF is compared to Stribild® (STB), as initial treatment of HIV-infection in ART-naive patients. This is a single-variable clinical comparison of the 2 tenofovir prodrugs, TAF and TDF

- **GS-US-292-0104** and **GS-US-292-0111**, Phase 3 randomized, double-blinded studies of the safety and efficacy of E/C/F/TAF versus E/C/F/TDF in HIV-1 infected, antiretroviral treatment-naive adults. The interim Week 48 key conclusions from pooled data are as follows: 1) E/C/F/TAF once daily was noninferior to STB once daily when administered for 48 weeks to HIV-infected, ART-naive adults, as assessed using the US Food and Drug Administration (FDA)-defined snapshot algorithm with HIV-1 RNA < 50 copies/mL (E/C/F/TAF 92.4%; STB 90.4%; difference in percentages: 2.0%, 95% CI: −0.7% to 4.7%), 2) administration of E/C/F/TAF resulted in > 90% lower plasma TFV and higher intracellular TFV-DP relative to STB, 3) E/C/F/TAF showed an improved renal and bone safety profile with significantly less decline in hip and spine BMD, less increase in serum creatinine and reduction in estimated glomerular filtration rate (eGFR), 4) Increases from baseline in fasting total cholesterol fasting low density lipoprotein (LDL) cholesterol, and fasting triglycerides were noted in the E/C/F/TAF group;

- **GS-US-292-0112**, a Phase 3 open-label safety study of E/C/F/TAF in HIV-1 positive patients with mild to moderate renal impairment; Week 48 results demonstrated that patients who switched to E/C/F/TAF had no change in eGFR, and had significant improvements in measures of renal function including proteinuria, albuminuria, retinol binding protein and beta-2-microglobulin. These subjects also had improvements in measures of bone mineral density. Importantly, because FTC was given without dose adjustment to patients with eGFR 30-50 mL/min, these patients had comparable safety profile to patients with eGFR 50-69 mL/min, with no increased rate of potential FTC related drug reactions, supporting the safety of FTC at higher exposures. In addition, 92% of study participants maintained virologic suppression (HIV-1 RNA < 50 copies/ml) at Week 48 after switching to E/C/F/TAF.

- **GS-US-292-0109**, a Phase 3 study designed to evaluate the safety, efficacy, and tolerability of switching to E/C/F/TAF in individuals who are virologically suppressed on regimens containing TDF. The interim Week 48 key conclusions from this study are as follows: 1) switching to E/C/F/TAF was noninferior to maintaining FTC/TDF+3rd Agent (STB, efavirenz/emtricitabine/tenofovir DF (ATR), atazanavir (ATV)/boosted+Truvada®) as assessed using the FDA snapshot algorithm (Week 48 FAS) with HIV-1 RNA cutoff at 50 copies/mL (E/C/F/TAF 95.6%; FTC/TDF+3rd Agent 92.9%; difference in percentages: 2.7%, 95.01% CI: −0.3% to 5.6%), 2) An improved renal and bone safety profile was observed in subjects who switched to E/C/F/TAF, 3) there were no differences in ocular findings between treatment groups and no reported cases of uveitis.

1.3. Rationale for This Study

Because of the increasing average age of HIV-infected patients, the high prevalence of chronic kidney disease, and the increasing prevalence of co-morbid conditions that require medical management, medical regimens in ESRD patients are complex and can impact a patient's overall risk of morbidity and mortality. The availability of a single-tablet regimen composed of potent agents with improved tolerability and long-term safety that does not require dose adjustment at eGFR < 15 mL/min, would represent an important therapeutic innovation for HIV infected patients with ESRD. EVG, COBI, and TAF are not renally eliminated, while the metabolite of TAF (TFV) and FTC, are renally eliminated.

The E/C/F/TAF FDC was recently shown to be safe and efficacious in HIV-infected patients with mild to moderate chronic kidney disease (CKD; eGFR 30-69 mL/min) in study GS-US-292-0112 through 48 weeks. The long-term safety of E/C/F/TAF remains to be established in subjects at more advanced stages of renal impairment, including those with ESRD on hemodialysis. The present study will provide the pharmacokinetic data describing TFV and FTC exposures in these patients when administered as the E/C/F/TAF FDC, dosed once daily, as well as safety and efficacy data in this special population through 48 weeks.

1.3.1. Rationale for Dose Selection

The E/C/F/TDF FDC containing EVG (150 mg), COBI (150 mg), FTC (200 mg), and TAF (10 mg), is currently under review for use once daily for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older without any known resistance to the individual components and with an eGFR ≥ 30 mL/min. This FDC contains the equivalent doses of EVG and COBI in the marketed product, Stribild®. The FTC (200 mg) in the E/C/F/TAF FDC represents the marketed dose in several approved FDC products: emtricitabine/tenofovir DF, efavirenz/emtricitabine/tenofovir DF, and emtricitabine/rilpivirine/tenofovir DF for the treatment of HIV-1 infection.

EVG, COBI, and TAF are not renally eliminated, while the metabolite of TAF (TFV) and FTC, are renally eliminated.

TAF and TFV

The Phase 3 study GS-US-292-0112 demonstrated that patients with moderate renal impairment (baseline eGFR 30-50 mL/min) who switched to E/C/F/TAF had no change in eGFR, and had significant improvements in measures of renal function including proteinuria, albuminuria, retinol binding protein and beta-2-microglobulin. These subjects also had improvements in measures of bone mineral density. TAF PK in subjects with screening eGFR 30-69 mL/min was consistent with data following administration of E/C/F/TAF in nonrenally-impaired HIV-infected subjects in Phase 2 and Phase 3 studies.

Data from GS-US-120-0108 demonstrated that in HIV uninfected subjects with an eGFR of 15-29 mL/min, plasma TAF exposures increased < 2-fold. Study GS-US-292-1825 will evaluate TAF (as well as TFV and FTC) PK in the setting of daily administration of E/C/F/TAF STR in treatment-experienced subjects with eGFR < 15 mL/min on chronic hemodialysis.

To support TAF dosing in ESRD patients, simulation for TFV exposures was conducted using an established population pharmacokinetic model for TFV following administration of E/C/F/TAF and with information from previously conducted Gilead Study (GS-01-919) where TDF was administered in ESRD subjects (Figure 1-1).

Figure 1-1. Predicted Steady-State TFV PK Profile After Administration of E/C/F/TAF in ESRD Subjects on Chronic Hemodialysis

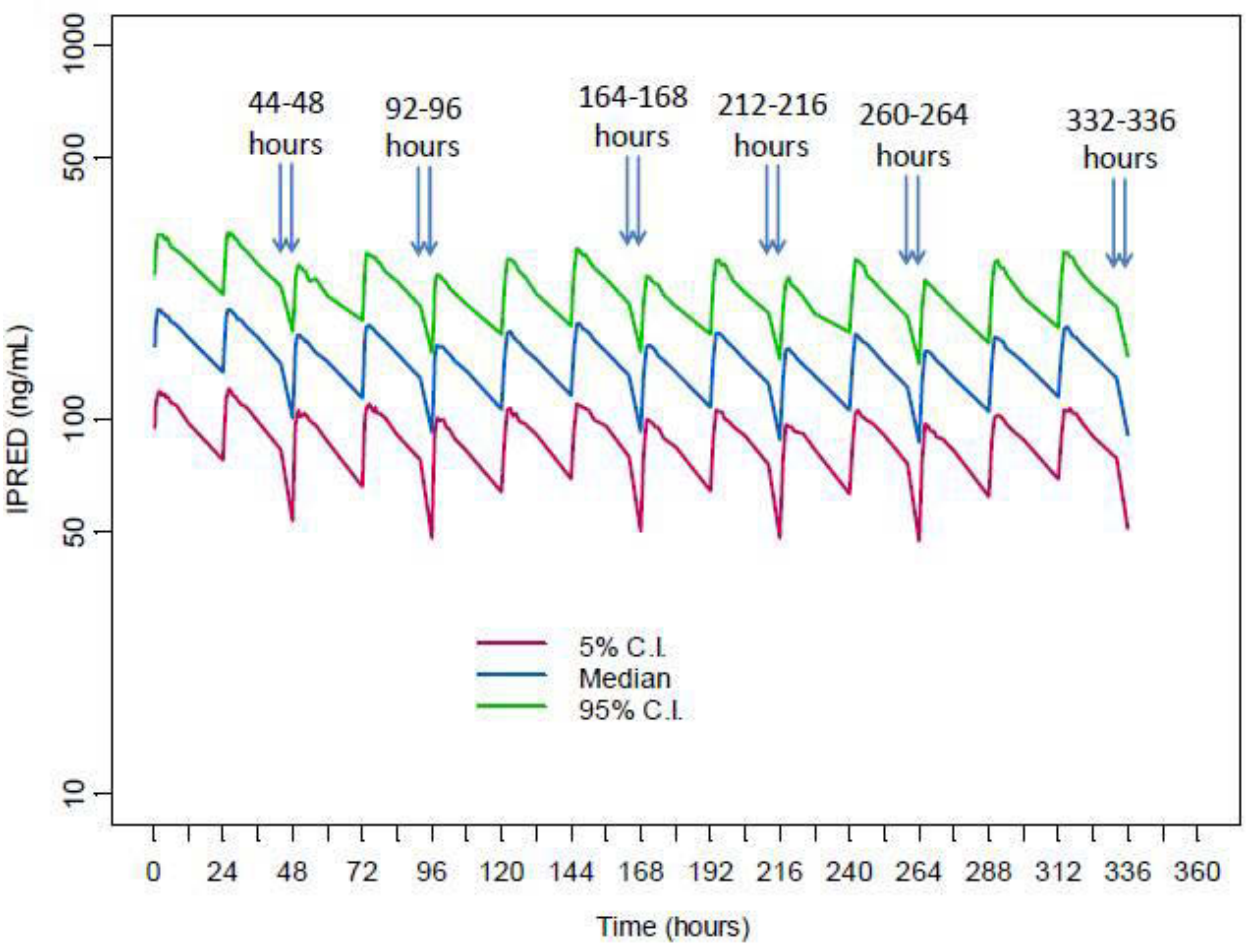


Figure 1-1 shows the simulated TFV PK profile following E/C/F/TAF once-daily for two weeks in subjects with ESRD on chronic hemodialysis three-times per week. IPRED represents the model predicted plasma concentration of TFV. The double blue arrows represent a four-hour hemodialysis session.

In subjects with ESRD on chronic hemodialysis three-times per week, systemic TFV exposures are expected to be higher following administration of E/C/F/TAF, relative to E/C/F/TAF in subjects with eGFR > 30 mL/min, due to the renal elimination pathway for TFV. In subjects with ESRD on chronic hemodialysis, E/C/F/TAF administered once daily is predicted to result in a mean (% CV) TFV exposure of 3610 (21.6) h•ng/mL. Given the extensive safety data available for TDF, TFV exposures follow administration of E/C/F/TAF in ESRD subjects on chronic hemodialysis are expected to be in the range of those following TDF-containing regimens in patients with normal renal function (Table 1-1) and, as such, would not require TAF dose modification.

Table 1-1. Comparison of Plasma TFV Exposures After Administration of E/C/F/TAF in ESRD Subjects on Chronic Hemodialysis Versus TDF-Containing Regimens in Patients with Normal Renal Function

	TFV AUC (Mean [%CV])
E/C/F/TAF regimen	3610 (21.6)
TDF-Containing Regimens in Normal Renal Function	
Atazanavir+Ritonavir[a]	3940 (30)
Darunavir+Ritonavir[b]	4630 (16)
Fosamprenavir+Ritonavir[c]	2930 (1780, 4280)
Lopinavir+Ritonavir[d]	3500 (27)
Saquinavir+Ritonavir[e]	3110 (24)
Rilpivirine[f]	3590 (22)
Emtricitabine+TDF[g]	2870 (25)
Efavirenz/Emtricitabine/TDF[h,i]	2270 (19)
Elvitegravir/Cobicistat/Emtricitabine/TDF[h]	3940 (20)

a Study GS-US-216-0114
b {11428}
c mean (90% CI); {15426}
d Studies 00-909 and 01-943
e Study GS-US-104-0236
f {8510}
g Studies GS-US-236-0101 and GS-US-236-0110
h Studies GS-US-236-0120
i Study GS-US-334-0131

FTC

The FTC dose (200 mg) in the E/C/F/TAF FDC represents the marketed dose as part of the approved products FTC (Emtriva®), FTC/TDF (Truvada®), efavirenz/FTC/TDF (Atripla®), FTC/rilpivirine/TDF (Complera® or Eviplera®), and E/C/F/TDF (Stribild®) for the treatment of HIV-1 infection. Emtricitabine is principally eliminated by the kidney and higher exposures are observed in patients with moderate to severe renal impairment. For eGFR of 30-49 mL/min, Emtriva prescribing information recommends dose interval adjustment of the 200 mg oral capsule to q48h. However, available clinical experience suggests the plasma FTC may not require dose adjustment in the setting of renal impairment. In study GS-US-292-0112, FTC was given without dose adjustment to patients with eGFR 30-50 mL/min, and these patients had comparable safety profile to patients with eGFR 50-69 mL/min, with no increased rate of potential FTC related drug reactions, supporting the safety of FTC at higher exposures.

In Study FTC-107, an open-label, parallel-group study of single-dose emtricitabine 200 mg in HIV uninfected subjects with varying degrees of renal impairment, 6 subjects with moderate renal impairment (30-49 mL/min), 5 subjects with severe renal impairment (< 30 mL/min) and 6 subjects on dialysis were treated. Of note, subjects with baseline eGFR of 30-49 mL/min had

only twice the mean FTC systemic exposure (mean (%CV) AUC_{inf}: 25.08 hr•µg/mL (23)) compared to subjects with eGFR > 80 mL/min (mean (%CV) AUC_{inf}: 11.78 (25) hr•µg/mL. Subjects on dialysis had an AUC_{inf} of 53.22 hr•µg/mL (19). In all cohorts, the overall incidence of adverse events was low and there was no apparent relationship between the incidence of AEs and the degree of renal impairment.

In study GS-US-104-0235, the safety and tolerability of FTC+TDF (200/300 mg) in treatment-naïve and treatment-experienced HIV infected subjects with various degrees of renal impairment were assessed. One subject in this study assigned to the mild impairment group was later found to have moderate impairment (eGFR ≥ 30 and < 50 mL/min) and one subject assigned to moderate impairment was found to have severe impairment (eGFR < 30 mL/min) after 40 days of treatment. Based on PK analyses of these subjects, the subject with moderate renal impairment was continued on FTC 200 mg daily because FTC exposures remained within the predicted range for subjects without renal impairment and the subject with severe renal impairment continued to receive FTC 200 mg every 48 hours based upon appropriate FTC systemic exposures.

Consistent with the renal impairment Study FTC-107 described above, results from the PK sub-study of GS-US-292-0112 (n = 30) showed that FTC exposure was slightly higher in subjects with mild to moderate renal impairment as compared with historical data on FTC in subjects with normal renal function (mean [%CV] FTC AUC_{tau} 20968.6 [25.5] ng•h/mL versus 11,714.1 [16.6] ng•h/mL in Phase 2 Study GS-US-292-0102 of non-renally-impaired HIV-infected subjects), as expected due to the renal elimination of FTC. Further population PK analysis on all subjects treated in Study GS-US-292-0112 with available FTC data (n = 241), confirmed the findings from the PK sub-study, showing slightly higher FTC exposures in subjects with baseline $eGFR_{CG}$ < 50 mL/min, as compared with subjects with baseline $eGFR_{CG}$ ≥ 50 mL/min. Importantly, these observed differences in FTC exposure by renal impairment subgroup did not result in a different safety profile. The incidence of adverse events that occurred in ≥ 5% of subjects and of treatment-related adverse events that occurred in ≥ 1% of subjects was similar between groups after 48 weeks of treatment. Adverse reactions from the Emtriva SmPC were also specifically evaluated. Despite higher FTC exposure in this study, incidence of these events was similar in subjects with $eGFR_{CG}$ < 50 mL/min and in subjects with $eGFR_{CG}$ ≥ 50 mL/min. The current study will evaluate FTC exposures and safety, and an IDMC will be convened to monitor safety data.

1.4. Risk/Benefit Assessment for the Study

Potential risks of a patient's study involvement include switching to an unfamiliar regimen with potential loss of virologic control and/or new adverse events, the inconvenience of more frequent clinic visits and laboratory blood draws and the associated pain and discomfort of phlebotomy. Strategies to mitigate these risks include close monitoring of viral load, CD4+ T cell count and other lab values as well as monitoring of adverse events. Parameters for discontinuation of the study drug due to adverse events or lack of efficacy will be well-defined and closely followed. In addition, an independent data monitoring committee will be convened at Week 12 to evaluate safety data and determine whether the risks/benefits warrant continuation of the study.

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 and tolerability of E/C/F/TAF FDC in HIV-1 infected adults with ESRD on chronic HD at Week 48

The secondary objectives of this study are:

- To evaluate the proportion of subjects achieving virologic response (defined as HIV-1 RNA < 50 copies/mL, Snapshot analysis) at Weeks 24 and 48

- To evaluate plasma pharmacokinetics (PK) of EVG, COBI, FTC, TAF and TFV in HIV-1 infected patients with ESRD on HD

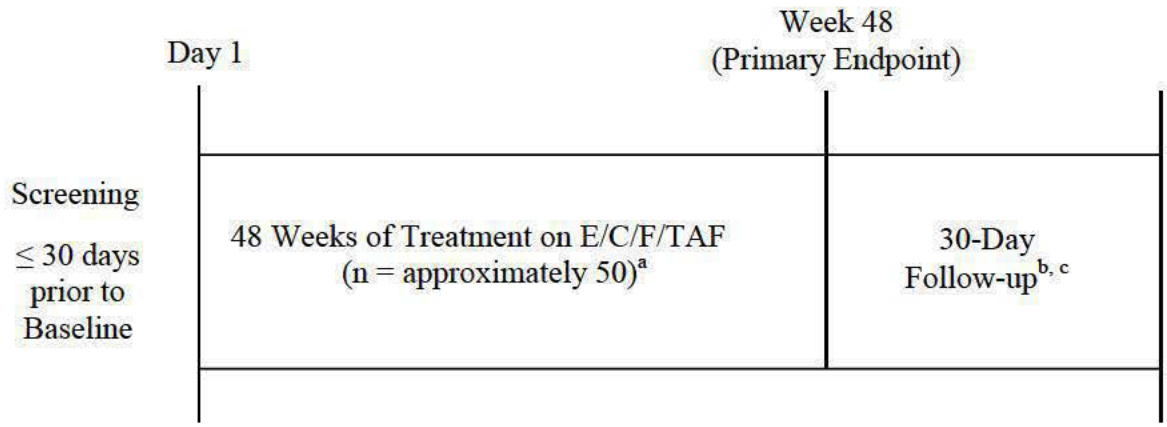
3. STUDY DESIGN

3.1. Study Design

This is an open-label, multicenter, single-arm study to assess the safety, tolerability, pharmacokinetics, and efficacy of E/C/F/TAF FDC in HIV-1 infected adult subjects with ESRD on chronic HD.

Approximately 50 subjects with ESRD on chronic HD will be enrolled. All subjects will switch from their current antiretroviral regimen to E/C/F/TAF on Day 1. The total treatment duration will be 48 weeks. After Week 48 visit, all subjects will stop study drug and complete a 30-Day Follow-up visit.

Figure 3-1. Study Schema



a Following the Day 1 visit, subjects will return for study visits at Weeks 2, 4, 8, 12, 24, 36 and 48.
b After 48 weeks, subjects will stop study drug and complete a 30-Day Follow-up visit to end their participation in the study.
c Subjects who discontinue study drug administration before their Week 48 visit, will complete and ESDD visit. These subjects may remain on the study off study drug up to the Week 48 visit. Upon completion of Week 48 visit, subjects may be required to return to the clinic for a 30-Day Follow-up visit to complete their participation in the study.

3.2. Study Treatments

Subjects who provide written consent and meet all eligibility criteria will receive elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF), on Day 1.

Study drug will be administered orally once daily with food at approximately the same time every day. On the day of hemodialysis, study drug administration should occur after completion of hemodialysis.

3.3. Duration of Treatment

The study will consist of a 30-day screening period (within 30 days before Day 1 visit), followed by a 48 weeks treatment period. After Day 1, subjects will return for study visits at Weeks 2, 4, 8, 12, 24, 36 and 48.

After Week 48, subjects will stop study drug and complete a 30-Day Follow-up visit.

3.4. End of Study

End of the study will occur when the last subject enrolled in the study has completed Week 48 visit followed by a 30-Day Follow-up visit.

3.5. 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.

3.6. Source Data

Sponsor will provide source document worksheets for all study visits.

3.7. PPD

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 50 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 screening procedures

2) Age ≥ 18 years

3) Currently receiving a stable antiretroviral regimen for ≥ 6 consecutive months prior to screening

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

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

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

5) No documented history of HIV-1 resistance to EVG, FTC, 3TC or TFV and no history of switching off EVG, FTC, 3TC or TFV due to concern for resistance

6) CD4+ T cell count of ≥ 200 cells/μL

7) ESRD with eGFR < 15 mL/min by Cockcroft-Gault formula for creatinine clearance {2202}

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

8) On chronic HD for ≥ 6 months prior to screening

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

10) Chronic Hepatitis C (HCV) infection allowed if liver function is stable for ≥ 6 months prior to screening: ALT ≤ 10 × ULN, AST ≤ 10 × ULN, total bilirubin ≤ 2.5, or normal direct bilirubin (subjects with documented Gilbert's Syndrome or hyperbilirubinemia due to atazanavir therapy may have total bilirubin up to 5 × ULN), INR ≤ 1.5 and albumin ≥ 3 g/dL; no evidence of cirrhosis or hepatocellular carcinoma by imaging in the last 12 months

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

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

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

    a) Not pregnant confirmed by a negative serum pregnancy test (unless permanently sterile or greater than two years post-menopausal)

    b) Of non-child bearing potential (i.e. women who have had a hysterectomy, have had both ovaries removed or medically documented ovarian failure, or are postmenopausal women > 54 years of age with cessation (for ≥ 12 months) of previously occurring menses

       Female subjects who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure must have a serum follicle stimulating hormone (FSH) level at screening within the post-menopausal range based on the Central Laboratory Reference range.

    c) Of childbearing potential and agrees to utilize the protocol specified method of contraception or be non-heterosexually active or practice abstinence from screening throughout the duration of the study treatment and for 30 days following study drug discontinuation (as defined in Appendix 6)

    d) Female subjects who utilize hormonal contraception as one of the birth control methods must have used the same method for at least three months prior to the study dosing.

14) Male subjects must agree to use protocol specified method(s) of contraception from screening throughout the duration of study treatment and for 30 days following discontinuation of study drugs (Appendix 6).

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

16) Lactating females must agree to discontinue nursing before the study drug is administered.

4.3. Exclusion Criteria

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

1) Hepatitis B surface antigen (HBsAg) positive

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

3) Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of screening

4) Treatment with radiation, cytotoxic chemotherapeutic agents, or any immunomodulator within 30 days of screening

5) Any other clinical history, condition, or test result that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements

6) Administration of other investigational agents (unless approved by Gilead Sciences). Participation in any other clinical trial, including observational trials, without prior approval from the sponsor is prohibited while participating in this trial.

7) History or presence of allergy or intolerance to the study drugs or their components

8) A new AIDS-defining condition (excluding CD4+ T cell count and percentage criteria) diagnosed within the 30 days prior to screening, with the exception of oropharyngeal candidiasis (see Appendix 7)

9) Have an implanted defibrillator or pacemaker

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

11) A history of malignancy within the past 5 years (prior to screening) or ongoing malignancy other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive carcinoma

12) Received solid organ or bone marrow transplant

13) Significant bone disease (e.g., osteomalacia, chronic osteomyelitis, osteogenesis imperfecta, osteochrondroses), or multiple bone fractures

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

15) Systemic chemotherapeutic agents, systemic corticosteroids (except short-term use of prednisone as a steroid burst [≤ 1 week of use]), immunosuppressant, or immunomodulating agents

16) Subjects receiving ongoing therapy with any of the following medications in the Table 4-1 below, including drugs not to be used with EVG, COBI, FTC, TAF

Table 4-1. Disallowed Agents

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

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

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

This is an open-label, single arm study. All eligible subjects will receive open-label E/C/F/TAF.

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

It is the responsibility of the Investigator to ensure that the subject is eligible for the study prior to enrollment. Once eligibility is confirmed, each subject will be assigned a unique subject number using Interactive Web Response System (IWRS). Once a subject number has been assigned to a subject, it will not be reassigned to any other subject. The subject number assignment may be performed up to 3 days prior to the in-clinic Day 1 visit, provided that all other screening procedures have been completed and subject eligibility has been confirmed.

Eligibility must be confirmed and all Day 1 tests and procedures must be completed prior to the administration of the first dose of study drug.

IWRS will assign study drug bottle numbers at each study visit. Initiation of study drug must take place on the day of Day 1 visit.

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

5.2.1. Formulation

E/C/F/TAF 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).

The E/C/F/TAF tablet core contains 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 packaging material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed, aluminum-faced liner.

Study drug to be distributed to centers in the US and other 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

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

E/C/F/TAF FDC tablets containing 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF will be provided to all eligible subjects at Day 1. Study drug will be administered orally at approximately the same time each day with food.

On the day of hemodialysis study drug administration should occur after completion of completion of hemodialysis.

Subjects will be instructed to bring all study drug in the original container at each clinic visit for drug accountability (unless otherwise specified in the study procedures sections of this protocol). The Investigator will be responsible for maintaining accurate records for all study drug bottles dispensed and tablets returned. The 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.

5.4. Prior and Concomitant Medications

- For subjects receiving hormonal contraceptives, investigators and/or the subject's healthcare providers should consider additional methods of contraception, as concentrations of ethinyl estradiol may decrease and progestin level may increase on co-administration with study drug.

- The use of medications for the treatment of HIV, other than study drug, is prohibited.

- For subjects receiving concomitant medications that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious adverse events, investigators and/or the subject's healthcare providers should consider alternative concomitant medications.

- During the study, subjects may not receive any of the following concomitant medications:

  — Competitors of renal excretion (e.g., probenecid; high-dose non-steroidal anti-inflammatory drugs)

  — Known nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, vancomycin, cidofovir, foscarnet, cisplatin and pentamidine)

- 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. Any concomitant medication requiring adjustment or discontinuation due to renal impairment or a change in renal function on study should be managed per that drug's prescribing information.

Table 5-1. Prior and Concomitant Medications

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

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

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

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

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

5.5. Accountability for E/C/F/TAF

The Investigator is responsible for ensuring adequate accountability of all used and unused study drug. Accountability records (Study Drug Inventory Log) will be provided to each study site in order to:

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

The Investigator [or designee (e.g., study center pharmacist)] will acknowledge receipt of the study drugs from Gilead Sciences (or designee) after reviewing the shipment's content and condition. The Investigator (or designee) will be responsible for maintaining an accurate inventory of the dates and quantities of all study drugs received, dispensed, and returned. Subjects should be instructed to return all unused study drug to the site at their study visits.

Each dose of the study drug administered at the study center will be administered by qualified study center personnel. All doses of study drug administered to subjects in the clinic under the supervision of staff will be accurately recorded on the Study Drug Inventory Logs provided by Gilead Sciences (or on equivalent documentation maintained by the study center), which indicates the date and quantity of all doses of study drug dispensed to individual subjects. The requirements of all applicable drug dispensing laws will apply to all doses of study drugs dispensed by the Investigator (or designee).

The study drug inventory log 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.

5.5.1. Study Drug Return or Disposal

The study monitor will provide instructions to the sites regarding the return of used and unused study drug. 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. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused study drug bottles in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

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

The investigator must document any deviation from protocol procedures in the subject's source documents and electronic Case Report Forms (eCRFs). In addition, the Sponsor and the 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 each subject is eligible for the study before enrollment.

Subjects who provide written consent and meet all eligibility criteria will receive elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF), on Day 1. Please refer to Section 5.1 for details about enrollment and treatment assignment.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

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

- Obtain written informed consent
- Obtain medical history including history of HIV-1 disease-related events, substance use, family history of cardiovascular disease (i.e. myocardial infarction, stroke, peripheral vascular/arterial disease, and/or angina) and prior medications within 30 days of the screening visit
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate and temperature) and weight
- 12-lead ECG performed supine
- Height

- Blood sample collection for the following laboratory analyses:

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

  — FSH test is required for female subjects who have stopped menstruating for > 12 months but do not have documentation of ovarian hormonal failure.

  — Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, PT/INR, amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) and parathyroid hormone (PTH)

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

  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)

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

  — CD4+ T cell count

  — Plasma HIV-1 RNA (Taqman v2.0)

  — Hepatitis B virus surface antigen serology (HBsAg)

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

- HIV-TSQs (HIV Treatment Satisfaction Questionnaire Status) should be completed by the subject. Subject is to read the questionnaire by him/herself and write/mark answers directly onto the questionnaire.

- Review of AEs and concomitant medications (adverse events related to protocol mandated procedures occurring after signing of the consent form)

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

From the time of obtaining informed consent through the first administration of study drug, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (eCRF). All other

untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Day 1 Assessments

The following evaluations are to be completed after confirmation of eligibility, and before the study drug is dispensed to the subject. Initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit.

- Obtain subject number and study drug bottle assignment from IWRS. The subject number assignment and enrollment 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.
- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs (blood pressure, pulse, respiration rate, and temperature) and weight
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, phosphorus, magnesium, potassium, sodium, uric acid, amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) and PTH
  - Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula for creatinine clearance
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Plasma HIV-1 RNA (Taqman v2.0)
  - CD4+ T cell count
  - Whole blood storage sample collection for virology analyses

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

— Serum and plasma storage samples for possible additional clinical testing (for subjects who provide consent)

— Serum pregnancy test (females of childbearing potential only)

- SF-36, VAS and HIV-TSQs should be completed by the subject. Subject is to read the questionnaire by him/herself and write/mark answers directly onto the questionnaire.
- Site-administered questions for Health Utilization Assessment to be completed
- Study drug dispensation. Study drug will be dispensed in an open-label fashion. Subjects must initiate dosing of study drug on the day of the Day 1 visit.
- Subjects should be instructed to take E/C/F/TAF FDC tablets once daily with food at the same time each day. On the days of hemodialysis, subjects should be instructed to take study drug after completion of hemodialysis. Subjects should also be counseled regarding the importance of adherence and taking their study drugs at approximately the same time each day.

6.3. Treatment Assessments (Weeks 2-48)

All study visits are to be scheduled relative to the Day 1 visit date. Study visits are to be completed within ± 2 days of the protocol-specific visit date through Week 12 and completed within ± 6 days of the protocol-specific visit date through Week 36. The visit window at Week 48 will be ± 6 weeks of the protocol-specific visit date, and this clinical visit window coincides with the Week 48 statistical analysis window for HIV RNA. Unless notified by the Sponsor, Week 48 visit should be completed within ± 6 days of the protocol-specific visit date.

The following evaluations are to be completed at the end of Weeks 2, 4, 8, 12, 24, 36 and 48 unless otherwise specified.

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

- Pre-dose (within 30 minutes prior to study drug administration) whole blood samples collection for plasma and PBMC samples (**Week 4 or Week 12 only**).

  Note: Week 4 or Week 12 visit should occur on the day of hemodialysis for this sample collection. Study drug administration should occur after completion of hemodialysis and should be observed on-site.

  — PBMC sample processing will be performed by the central laboratory and plasma sample processing will be performed on-site. Details of the blood sampling procedures and sample management will be documented in the central laboratory manual.

- All subjects who are willing to consent will be eligible to participate in the pharmacokinetic sub-study (target n = 15) at or between Week 2 or Week 4 study visits**,** on a day prior to the day of hemodialysis and when the subject has administered three doses of E/C/F/TAF between two hemodialysis sessions. E/C/F/TAF administration prior to post-dose blood sample collection will be observed in-clinic.

  — The ± 2 day window at Week 2 or Week 4 study visits does not apply to the PK sub-study visit. Please see Section 6.5.1 and Appendix 3, Pharmacokinetic (PK) Sub-study for additional details.

- Review of AEs and changes in concomitant medications
- Complete physical examination (**Weeks 24 and 48 only**) (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Symptom-directed physical examination as needed (**Weeks 2, 4, 8, 12 and 36**)
- Vital signs (blood pressure, pulse, respiration rate, and temperature) and weight
- Blood sample collection for the following laboratory analyses:

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

  Note: At Weeks 24 and 48, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.

  - Chemistry profile will include PT/INR only at Week 24 and Week 48.

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

  — Estimated glomerular filtration rate according to the Cockcroft-Gault formula for creatinine clearance

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

  — Plasma HIV-1 RNA (Taqman v2.0)

  - Subjects who meet the criteria for virologic rebound should be managed according to Management of Suspected Virologic Failure (Section 6.6.1).

— CD4+ T cell count

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

— Serum and plasma storage samples for possible additional clinical testing (for subjects who provide consent)

— Serum pregnancy test (females of childbearing potential only).

  - Serum pregnancy testing may be performed more frequently if required by local regulations.

- Subject completed questionnaires:

  — SF-36 completed at Weeks 24 and 48 only

  — HIV-TSQs completed at Weeks 4, 24 and 48. HIV-TSQc (HIV Treatment Satisfaction Questionnaire Change) completed at Weeks 24 and 48.

  — VAS completed at all visits

  The questionnaires should be completed by the subject. Subject is to read the questionnaire by him/herself and write/mark answers directly onto the questionnaire.

- Site-administered questions for Health Utilization Assessment to be completed

- Study drug dispensation (except at Week 2 and Week 48). Document study drug dispensation and accountability.

  — At Day 1, study drug will be dispensed for 30 days. At the Week 2 visit, study drug will not be dispensed.

  — At Week 48, study drug dispensation will not occur. Schedule the subject for a 30-Day Follow-Up visit.

  Note: At the Week 2 visit, provide the scheduled Week 4 visit date to the subject. Week 4 visit should occur on day of hemodialysis. Instruct the subject to take study drug at Week 4 on-site (after completion of hemodialysis).

- Subjects should be instructed to take E/C/F/TAF FDC tablets once daily with food at the same time each day.

- Subjects should also be counseled regarding the importance of adherence and taking their study drugs at approximately the same time each day.

6.4. Post-treatment Assessments

6.4.1. 30-Day Follow-up Assessments

Subjects who complete the study through the Week 48 visit will be required to return to the clinic for a 30-Day Follow-Up Visit.

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

Subjects who permanently discontinue study drug prior to the Week 48 visit and refuse to continue in the study through the Week 48 visit will be asked to return to the clinic 30 days after the completion of the ESDD Visit for the 30-Day Follow-Up Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used. The following evaluations are to be completed at the 30-Day Follow-Up Visit:

- Review of AEs and changes in concomitant medications
- Symptom-directed physical examination as needed
- Weight
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) and PTH.
  - Hematology profile: CBC with differential and platelet count
  - Plasma HIV-1 RNA (Taqman v2.0)
  - CD4+ T cell count
  - Serum pregnancy test (females of childbearing potential only)
  - Serum and plasma storage samples for possible additional clinical testing (for subjects who provide consent)

At the 30 Day Follow Up Visit, any evaluations showing abnormal results believed to be a reasonable possibility of a causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

6.4.2. Early Study Drug Discontinuation Assessments (ESDD)

If the subject discontinues study drug prior to the Week 48 visit, the subject will be asked to return to the clinic within 72 hours of stopping study drug for the ESDD visit.

Every attempt should be made to keep the subject in the study through Week 48 visit and continue to perform the required study-related follow-up and procedures (see Section 6.4.3, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

Subjects who permanently discontinue study drug prior to the Week 48 visit and refuse to continue in the study through Week 48 visit will be asked to return to the clinic 30 days after the completion of ESDD visit for the 30-Day Follow-up visit.

At the Early Study Drug Discontinuation Visit, any evaluations showing abnormal results indicating that there is a possible or probable causal relationship with the study drug, should be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

The following evaluations are to be completed at the Early Study Drug Discontinuation Visit

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- 12-lead ECG performed supine
- Vital signs (blood pressure, pulse, respiration rate, and temperature) and weight
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) and PTH
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Plasma HIV-1 RNA (Taqman v2.0)
    - Subjects who meet the criteria for virologic rebound should be managed according to Management of Suspected Virologic Failure (Section 6.6.1).

- CD4+ T cell count
- Plasma sample for virology testing or pharmacokinetic testing
- Serum and plasma storage samples for possible additional clinical testing (for subjects who provide consent)
- Serum pregnancy test (females of childbearing potential only)

- SF-36, HIV-TSQc and VAS questionnaires should be completed by the subject. Subject is to read the questionnaire by him/herself and write/mark answers directly onto the questionnaire.
- Site-administered questions for Health Utilization Assessment to be completed
- Drug accountability

6.4.3. 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
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 6
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.5. Other Evaluations

6.5.1. Pharmacokinetic (PK) Sub-study

All subjects who are willing to consent will be eligible to participate in the pharmacokinetic sub-study (target n = 15).

Intense blood sampling will be conducted at hours 0.5, 1, 2, 3, 4, 6, 8, and 24.

PK sub-study visit must occur at or between Week 2 or Week 4 study visits, on a day prior to the day of hemodialysis and when the subject has administered three doses of E/C/F/TAF between two hemodialysis sessions. The ± 2 day window at Week 2 or Week 4 study visits does not apply to the PK sub-study visit. Study drug administration will be observed in-clinic at the sub-study visit. The sub-study will include intensive PK profiling in plasma. Details of the blood sampling procedures and sample management will be documented in the central laboratory manual.

6.5.2. Blood Storage

From subjects who provide additional consent, a portion of the blood drawn at all visits (except the Screening Visit and Unscheduled Visits) will be frozen and stored. These stored blood samples may be used by the Sponsor or its research partners for future testing to learn more about how the study drug has worked against HIV-1 or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without expressed consent of study subjects. At the conclusion of this study, these samples may be retained in storage by Gilead Sciences, Inc. for a period up to 15 years.

6.6. Virologic Failure

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

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

6.6.1. Management of Virologic Failure

- If the viral load is ≥ 50 copies/mL, HIV-1 RNA should be repeated at a scheduled or unscheduled visit (2-4 weeks after the date of the original test with HIV-1 RNA ≥ 50 copies/mL).
- Upon confirmation of HIV-1 RNA ≥ 50 copies/mL, potential causes of virologic failure should be documented. Assessments should include:
  - Adherence
  - Concomitant medication
  - Comorbidities (for example: active substance abuse, depression, other intercurrent illnesses)
- If virologic rebound is confirmed, and the HIV-1 RNA is < 400 copies/mL, subjects may remain on their current regimen at the discretion of the Investigator. Subject will return for a repeat within 2-4 weeks.

- If virologic failure is confirmed at the scheduled or unscheduled visit and HIV-1 RNA value is ≥ 400 copies/mL, the blood samples from the confirmation visit will be used for HIV-1 genotype/phenotype testing.

- If genotype/phenotype resistance to study drug is documented, study drugs should be discontinued.

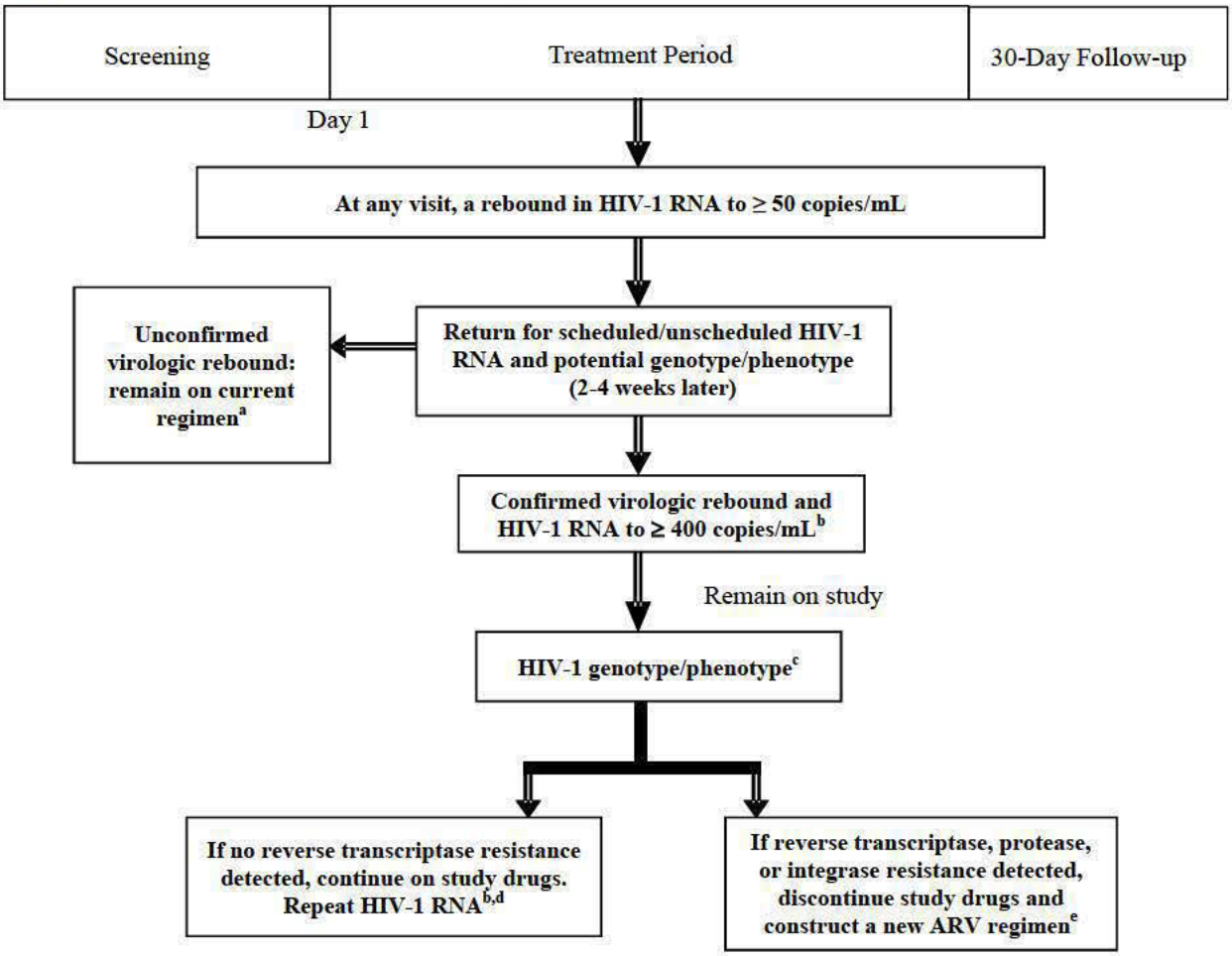
- If no resistance is detected from genotype/phenotype testing, subject may remain on study drug and HIV-1 RNA should be repeated (2-4 weeks from the date of confirmed test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug for each individual subject and document this assessment in the subjects source documents. Investigators who opt to discontinue study drugs for an individual subject must discuss with the Medical Monitor prior to study drug discontinuation.

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

Subjects with HIV-1 RNA < 50 copies/mL could subsequently experience unconfirmed blips of HIV-1 RNA ≥ 400 copies/mL. Such subjects will be analyzed for resistance if the unconfirmed rebound happens at Week 24 or Week 48, or at the last visit while receiving study drugs (or within 72 hours of discontinuation of study treatment).

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

Figure 6-1. Schema for Management of Virologic Failure



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

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)
- 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 (e.g., 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 (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.6.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

- **No:** Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., 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 (e.g., 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, (e.g., 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 5) 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 case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until 4 weeks after last administration of study drug must be reported to the eCRF database as instructed.

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

7.3.2. Serious Adverse Events

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

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

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

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 guideline.

Serious Adverse Event Paper Reporting Process

- Serious Adverse Event Paper Reporting Process (only to be used if EDC System is not available)

  — All SAEs will be recorded on the serious adverse event report form and submitted by faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of:

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

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 the SAE was reported via paper, it 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 the study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Special Situations Reports

7.5.1. Definitions of Special Situations

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

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

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

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

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only

when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

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

7.5.2. Instructions for Reporting Special Situations

7.5.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study 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 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 (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

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

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

Gilead DSPH contact information is as follows:

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

Refer to Appendix 6 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5.2.2. Reporting Other Special Situations

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

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

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

Refer to the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

7.6. Toxicity Management

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

- All clinically significant Grades 3 and 4 laboratory abnormalities should be repeated within 3 calendar days to confirm toxicity grade. Confirmation of toxicity grade is required prior to the next dose of study drug for any Grade 3 and 4 laboratory abnormality that in the opinion of the Investigator is clinically significant and may pose a risk to the subject's safety.

- Clinical events and clinically significant laboratory abnormalities will be graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (refer to Appendix 5).

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

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the Investigator.

7.6.2. 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.

- If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge 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.

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 3-4 laboratory abnormality (e.g., CK elevation after strenuous exercise, or triglyceride elevation that is non-fasting or that can be medically managed) or a Grade 3-4 clinical event considered unrelated to study drug.

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 and tolerability of the elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide (EVG/COBI/FTC/TAF; E/C/F/TAF) fixed dose combination (FDC) in HIV-1 infected adults with end stage renal disease (ESRD) on chronic hemodialysis (HD) at Week 48

The secondary objectives of this study are:

- To evaluate the proportion of subjects with virologic response (HIV-1 RNA < 50 copies/mL, Snapshot analysis) at Weeks 24 and 48

- To evaluate plasma pharmacokinetics (PK) of EVG, COBI, FTC, TAF and TFV in HIV-1 infected patients with ESRD on HD

8.1.2. Primary Endpoint

The primary endpoint is the incidence of treatment-emergent grade 3 or higher adverse events at Week 48.

8.1.3. Secondary Endpoints

- Proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot algorithm

- The pharmacokinetics parameters of EVG, COBI, FTC, TAF and TFV, including AUC_{tau}/AUC_{last}, C_{max}, and C_{min} for the sub-study.

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Full Analysis Set

Full Analysis Set (FAS): The Full Analysis Set will include all the subjects who were enrolled and received at least one dose of study drug. The FAS will exclude subjects with major protocol violations. The FAS analysis set is the primary analysis set for the efficacy analyses.

8.2.1.2. Safety Analysis Set

The primary analysis set for safety analyses is defined as all subjects that received at least one dose of study drug.

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

8.2.1.3. Pharmacokinetics

The Pharmacokinetic (PK) analysis set will include all subjects in the safety analysis set who participated in the sub-study and for whom concentration data of any one analyte (e.g., TAF, EVG, COBI, TFV and FTC) of interest are available.

8.3. Demographic Data and Baseline Characteristics

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

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

Baseline data will include a summary of body weight, height, body mass index and HIV-1 infection.

8.4. Primary and Secondary Analysis

8.4.1. Primary Analysis

The primary endpoint is the incidence of treatment-emergent grade 3 or higher adverse events at Week 48. Treatment-emergent adverse events are defined in Section 8.5.2.

8.4.2. Secondary Analyses

The proportion of subjects achieving HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 will be computed using the FDA snapshot algorithm. The measures of pharmacokinetics of EVG, COBI, FTC, TAF and TFV, AUC, C_{max}, and C_{min}, will be summarized using descriptive statistics [N, mean, standard deviation, percent coefficient of variation (%CV), median, minimum, and maximum] for the sub-study.

8.5. Safety Analysis

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

All safety data collected on or after the date that study drug was first administered up to the date of last dose of study drug plus 30 days will be summarized. Data for pre-treatment period and the period post the date of last dose plus 30 days will be included in data listings.

8.5.1. Extent of Exposure

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

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. Dosing information for individual subjects will be listed.

8.5.2. Adverse Events

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

Treatment-emergent adverse events are 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. Additional summaries will include summaries for adverse events by grade, Investigator's assessment of relationship to study drug, and effect on study drug dosing.

8.5.3. Laboratory Evaluations

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

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

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. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment-emergent. The maximum toxicity grade will be summarized by laboratory parameter.

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

8.5.4. Other Safety Evaluations

Weight will be summarized by visit.

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

8.6. Pharmacokinetic Analysis

Pharmacokinetic parameters will be listed and summarized for using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Plasma concentrations of the study drug over time will be plotted in semi logarithmic and linear formats as mean ± standard deviation.

8.7. Sample Size

A sample size of approximately 50 subjects is based on practical considerations and is considered to be sufficient to evaluate the primary objective of this study. The Grade 3 or higher AE rate in Study GS-US-292-0112 in subjects that had mild to moderate renal impairment was 8.8% at Week 48 for the E/C/F/TAF arm. Therefore, with 50 subjects, and an assumed rate of Grade 3 or higher AEs being 10%, this study would provide 95% confidence for the primary endpoint to be (1.7%, 18.3%) assuming normal approximation to binomial proportions.

A sample size of at least 15 subjects is considered for estimating the PK parameters in the sub-study for practical reasons.

8.8. Data Monitoring Committee

An external multidisciplinary independent data monitoring committee (IDMC) will review the progress of the study and perform interim reviews of safety, efficacy data and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study drug warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The committee will convene after the first 25 subjects enrolled complete Week 12 of the study. The IDMC's specific activities will be defined by a mutually agreed charter, which will define the IDMC's membership, conduct and meeting schedule.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable sub-investigators 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 sub-investigator's) participation in the study. The investigator and sub-investigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

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

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

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

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

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is completed in EDC. The Inclusion/Exclusion Criteria and Enrollment eCRFs 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. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. 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 of used and unused study drug. If return is not possible, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

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

The study monitor will review study drug inventory 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, IRBs or IECs, or regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

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Appendix 1. Investigator Signature Page

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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 3b Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of E/C/F/TAF Fixed Dose Combination (FDC) in HIV-1 Infected Subjects on Chronic Hemodialysis

GS-US-292-1825, Amendment 1, 13 October 2015

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

PPD

Devi SenGupta
Devi SenGupta, MD (Printed)
Medical Monitor

10/14/15
Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed) _____ Signature _____

Date _____ Site Number _____

Appendix 2. Study Procedures Table

Study Procedure	Screen[a]	Day 1[b]	Week 2 to Week 48[c]							30-Day Follow-up[d]	ESDD[e]
			2	4	8	12	24	36	48		
Written Informed Consent	X										
Medical History	X										
Complete Physical Examination[f]	X	X					X		X		X
Symptom-directed Physical Examination[g]			X	X	X	X		X		X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X[h]	X
Height	X										
12-Lead ECG	X								X		X
Chemistry Profile[i]	X	X	X	X	X	X	X	X	X	X	X
Metabolic Assessments[j]		X					X[j]		X[j]		
Serum Pregnancy Test[k]	X	X	X	X	X	X	X	X	X	X	X
CD4+ T Cell Count	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA[l]	X	X	X	X	X	X	X	X	X	X	X
HIV-1 Genotype/Phenotype[m]			X	X	X	X	X	X	X		X
Estimated eGFR	X	X	X	X	X	X	X	X	X		X
Hematology profile[n]	X	X	X	X	X	X	X	X	X	X	X
Plasma Storage Samples		X	X	X	X	X	X	X	X		X
Serum and Plasma Storage Samples[o]		X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
HBV and HCV Serology[p]	X										
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
SF-36[q]		X					X		X		X

Study Procedure	Screen[a]	Day 1[b]	Week 2 to Week 48[c]							30-Day Follow-up[d]	ESDD[e]
			2	4	8	12	24	36	48		
HIV-TSQ[q]	X	X		X			X		X		X
VAS		X	X	X	X	X	X	X	X		X
Health Utilization Assessment[r]		X	X	X	X	X	X	X	X		X
Drug Dispensation and Accountability		X	X[s]	X	X	X	X	X	X[s]		X[s]
Pre-dose Whole Blood Sample Collection[t]				X		X					
Post-dose PK Sub-study[u]				X	X						
Whole Blood Storage Sample[v]		X									

a Evaluations to be completed within 30 days prior to Day 1.
b Subjects will be dispensed study drug on the Day 1 visit; initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit.
c All study visits are to be scheduled relative to the Day 1 visit date. Visit windows are ± 2 days of the protocol specified date through Week 12, ± 6 days of the protocol specified date through Week 48, except Week 48. Weeks 48 visit window is ± 6 weeks of the protocol specified date. Week 48 visit should be completed within ± 6 day window, unless otherwise specified by the Sponsor.
d Required for those subjects who complete Week 48 visit or those subjects who permanently discontinue study drug and do not continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.
e Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through Week 48, if the subject discontinues study drug prior to completion of Week 48 visit.
f Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator).
g Symptom-directed physical examination as needed
h Weight only
i Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, PT/INR, amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) and PTH. 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. PT/INR will be included in the chemistry profile at Screening, Weeks 24 and 48 only.
j Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments. At Weeks 24 and 48 analyses of glucose will be done as part of fasting metabolic assessments and not as part of the chemistry profile.
k Females of childbearing potential only. FSH test is required for female subjects who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
l If the HIV-1 RNA value is ≥ 50 copies/mL a retest should be collected at a scheduled or unscheduled visit, 2-4 weeks after the date of the original test (except for screening and baseline results). See Section 6.6.1.
m HIV-1 genotype/phenotype resistance testing only conducted for subjects with confirmed virologic rebound with HIV-1 RNA value ≥ 400 copies/mL. Subjects should be managed according to the Virologic Rebound Schema (Section 6.6.1). HIV-1 genotype/phenotype sample collection to occur if subjects HIV-1 RNA lab values meet the criteria described in this section.

n CBC with differential and platelet count
o For subjects who provide consent − serum and plasma storage samples for possible future testing will be collected.
p See Section 4.2 to confirm subject eligibility prior to enrollment.
q SF-36 is to be completed by subjects at Day 1, Week 24 and Week 48 visits. HIV-TSQs should be completed by the subjects at Screening, Day 1, Week 4, Week 24, Week 48 and ESDD visits. HIV-TSQc should be completed by the subjects at Week 24, Week 48 and ESDD visits.
r Subjects will be asked about their health utilization at Day 1 visit and every visit thereafter, including the ESDD and Unscheduled Visits.
s Drug accountability only; study drug will not be dispensed at these visit.
t At Week 4 or Week 12, pre-dose whole blood sample will be collected for subjects enrolled in the study. Sample collection should occur within 30 minutes prior to the study drug administration which should be observed on-site. PBMC processing will be completed by the central laboratory.
u At or between Week 2 or Week 4 study visits on a day prior to the day of hemodialysis and when the subject has administered three doses of E/C/F/TAF between two hemodialysis sessions. The ± 2 day window at Week 2 or Week 4 does not apply to the PK sub-study visit. Subjects who are willing to consent will be eligible to participate in the pharmacokinetic sub-study (target n = 15). Please see Section 6.5.1 and Appendix 3 Pharmacokinetic (PK) Sub-study for additional details.
v Whole blood storage sample collected at baseline visit for virology assessments.

Appendix 3. Pharmacokinetic Sub-study

Blood Sampling Time Points for Intensive PK:

	Time Point (hrs) Post-dose							
Study Day	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**24**
At or between Week 2 or Week 4	X	X	X	X	X	X	X	X

1) All subjects who are willing to consent will be eligible to participate in the pharmacokinetic sub-study (target n = 15).

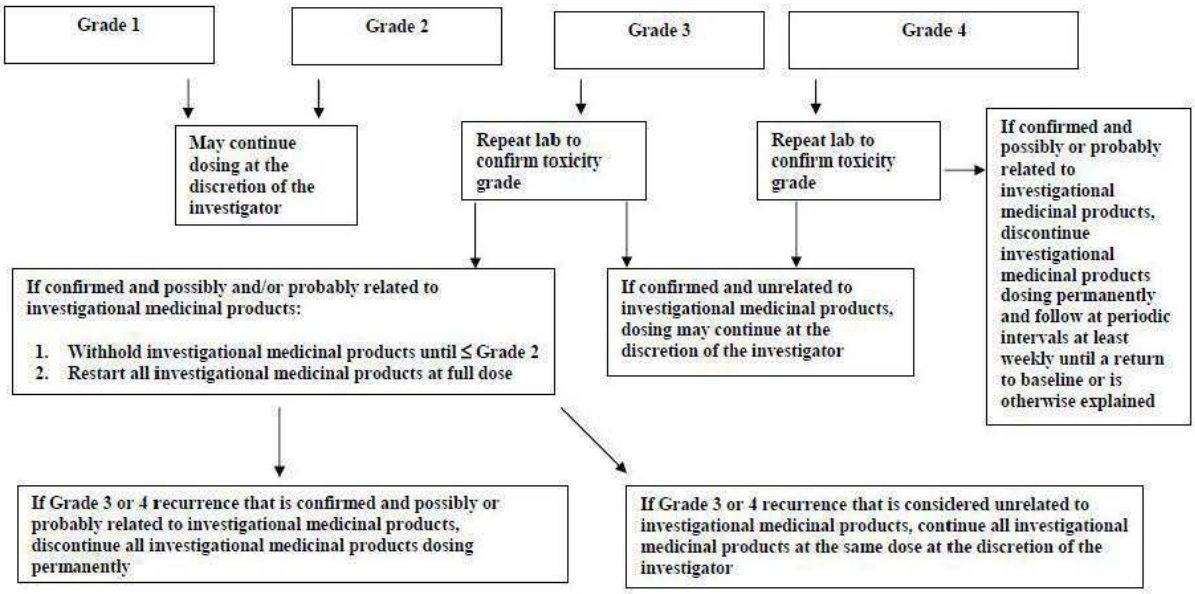
2) PK sub-study visit must occur at or between Week 2 or Week 4 on a day prior to the day of hemodialysis and when the subject has administered three doses of E/C/F/TAF between two hemodialysis sessions.

3) Study drug administration should be observed at the clinic prior to the 0.5 hour post-dose blood sample collection.

4) Subject should be instructed to dose after the 24 hour post-dose blood sample collection is collected and after the completion hemodialysis.

5) The sub-study will include intensive PK profiling in plasma. Details of the blood sampling procedures and sample management will be documented in the central laboratory manual.

Appendix 4. Management of Clinical and Laboratory Adverse Events



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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
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)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL.
** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects > 70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

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

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

Notes:

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

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

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

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

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

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

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/ Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/ Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
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 weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

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

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

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

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

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

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

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

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

Appendix 6. 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. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

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

b) Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

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

b) Contraception Requirements for Female Subjects of Childbearing Potential

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

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

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below:

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

  — Tubal sterilization

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

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

  Or

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

  — Barrier methods

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

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

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

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

3) Contraception Requirements for Male Subjects

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

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30days 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, partner pregnancy, and pregnancy outcome are outlined in Section 7.5.2.1.

Appendix 7. Definitions of HIV-1 Related Disease (CDC Guidelines) {35184}

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

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

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