CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b Open-Label Pilot Study to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed Dose Combination (FDC) in Virologically-Suppressed HIV-1 Infected Adult Subjects Harboring the Archived Isolated NRTI Resistance Mutation M184V/M184I	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	111,007	
EudraCT Number:	2015-002710-74	
Clinical Trials.gov Identifier:	NCT02616029	
Indication:	HIV-1 Infection	
Protocol ID:	GS-US-292-1824	
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PROTOCOL SYNOPSIS

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Study Title:	A Phase 3b Open-Label Pilot Study to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed Dose Combination (FDC) in Virologically-Suppressed HIV-1 Infected Adult Subjects Harboring the Archived Isolated NRTI Resistance Mutation M184V/M184I
IND Number:	111,007
EudraCT Number:	2015-002710-74
Clinical Trials.gov Identifier:	TBD
Study Centers Planned:	Approximately 38 centers in Europe and North America
Objectives:	The primary objective of this study is as follows: To evaluate the efficacy of E/C/F/TAF fixed dose combination (FDC) after switching from a stable regimen consisting of FTC/TDF or ABC/3TC plus a third antiretroviral agent in maintaining HIV-1 RNA < 50 copies/mL at Week 12 (using pure virologic response) in subjects harboring the archived NRTI resistance mutation M184V and/or M184I in HIV-1 reverse transcriptase The secondary objectives of this study are as follows: To determine the safety and tolerability of E/C/F/TAF FDC in subjects switching from 2 NRTI plus third antiretroviral agent regimens To evaluate the development of new resistance mutations in subjects who develop virologic failure after switching to E/C/F/TAF FDC To determine the durability of efficacy at Weeks 24 and 48 in maintaining HIV-1 RNA < 50 copies/mL using pure virologic response (PVR)

Study Design:

Open-label, single arm, multicenter study to evaluate the efficacy and safety of switching to E/C/F/TAF FDC in HIV-1 infected adult subjects with HIV-1 RNA < 50 copies/mL harboring an archived isolated M184V and/or M184I mutation associated with NRTI resistance and who have been on a stable regimen consisting of FTC/TDF or ABC/3TC plus a third antiretroviral agent with HIV-1 RNA below the detection limit for ≥ 6 months at screening. Subjects will have no evidence of previous virologic failure on a PI/r or INSTI-based regimen (with or without resistance to either class of ARV). Subjects may have evidence of a prior virologic failure on an NNRTI plus 2 NRTI-based regimen. Prior treatment changes due to tolerability will be allowed as long as virologic failure was not the reason for treatment change and the subject remained continuously suppressed.

Part 1

In Part 1, the enrollment criteria will allow 50 subjects to enter the study if they have M184V and/or M184I in HIV-1 reverse transcriptase WITHOUT any other NRTI resistance mutation (including thymidine analogue-associated mutations (TAMs) [M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R], K65R, K70E, T69 insertion and Q151M mutation complex [A62V, V75I, F77L, F116Y, Q151M]).

After these subjects in Part 1 have undergone their Week 12 visit, an interim efficacy review will be done by an *internal* Data Monitoring Committee (Internal DMC) that is independent of the study team and the study conduct activities, to ensure the rate of virologic failure is not unacceptably high. A pure virologic response (PVR) of < 80% would be considered unacceptable; safety monitoring will be designed to assure that the true value of PVR is above 80%.

Part 2

If the rate of virologic failure in Part 1 is deemed acceptable, once the internal DMC officially completes the interim review, entry criteria will be expanded and the study will continue to Part 2.

In Part 2, the enrollment criteria will be expanded to allow 50 additional subjects to enter the study if they have M184V and/or M184I in HIV-1 reverse transcriptase WITH or WITHOUT 1 or 2 TAMs that include M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R (not including the K65R, K70E, T69 insertion, and/or Q151M mutation complex [A62V, V75I, F77L, F116Y, Q151M]).

	Safety Monitoring of Virologic Failures All HIV-1 RNA values will be reviewed on an ongoing basis. Any post-Day 1 HIV-1 RNA ≥ 50 copies/mL will be repeated within 2-4 weeks. Subjects with confirmed HIV-1 RNA ≥ 50 copies/mL will be managed in discussion with the Medical Monitor in accordance with guidelines developed for the E/C/F/TAF phase 3 program.
Number of Subjects Planned:	Approximately 100 subjects will be enrolled into the study.
Target Population:	HIV-1 infected adults (≥ 18 years) with HIV-1 RNA < 50 copies/mL on a stable regimen containing FTC/TDF or ABC/3TC plus an (allowed) third antiretroviral agent (refer to Table 4-1) for ≥ 6 consecutive months prior to screening and documented presence of NRTI resistance mutation M184V and/or M184I in HIV-1 reverse transcriptase.
Duration of Treatment:	A 42 day screening period followed by 48 weeks of treatment and a 30 Day Follow-Up visit after completion of study drug. Subjects that develop virologic failure will be followed for the duration of the study or longer to document virologic suppression on a revised regimen.
Diagnosis and Main Eligibility Criteria:	HIV-1 infected adult subjects who meet the following criteria will be given the option to participate in the study: • Documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 months preceding and at the screening visit (measured at least twice using the same assay). One unconfirmed virologic elevation or "blip" of ≥ 50 copies/mL after previously reaching viral suppression is acceptable. • Currently receiving an antiretroviral (ARV) regimen consisting of FTC/TDF or ABC/3TC plus a third antiretroviral agent for ≥ 6 consecutive months preceding the Screening visit. Refer to Table 4-1 for allowed third agents. • No previous use of any approved or experimental integrase strand transfer inhibitor (INSTI) (for any length of time) if the current regimen contains a PI/r.

All subjects must have a historical genotype report showing M184V and/or M184I (mixtures are acceptable) in HIV-1 reverse transcriptase WITHOUT (Part 1) and WITH or WITHOUT (Part 2) 1 or 2 TAMs. Subjects must not have any primary INSTI or primary PI resistance mutations. Additional NRTI resistance mutations not defined below are allowed, and NNRTI mutations are allowed (see Table 3-1).
Subjects identified as having the indicated resistance mutation profile from a historical genotype will then be tested for archived resistance by proviral genotype analysis (from whole blood) at screening visit. Proviral DNA tested must not have additional exclusion resistance mutations (defined in Table 3-1 for Part 1 or Part 2); if identified, subjects will be excluded from entry into the study.

- **Part 1 Resistance Criteria (first 50 subjects):** M184V and/or M184I (mixtures are acceptable) in reverse transcriptase WITHOUT any other NRTI resistance mutation (including TAMs [M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R], K65R, K70E, T69 insertion and Q151M mutation complex [A62V, V75I, F77L, F116Y, Q151M]).
- **Part 2 Resistance Criteria (second 50 subjects; after the interim efficacy review):** M184V and/or M184I (mixtures are acceptable) in reverse transcriptase WITH or WITHOUT 1 or 2 TAMs [M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R]. Evidence of K65R, K70E, T69 insertion and/or Q151M mutation complex [A62V, V75I, F77L, F116Y, Q151M] in addition to the resistance mutations above will not be eligible for entry into the study.

Must not have integrase or protease inhibitor (PI) mutations present on historical genotype. Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) mutations are allowed.

Estimated glomerular filtration rate ≥ 30 mL/min according to the Cockcroft-Gault formula for creatinine clearance

Study Procedures/ Frequency:

Following Screening, eligible subjects will be required to return for study visits at Day 1, Weeks 4, 8, 12, 16, 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.

Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count, and complete or symptom directed physical examinations will be performed at Screening, Day 1 and specific subsequent study visits.

	A whole blood sample will be collected at the Screening visit for proviral genotype analysis for archived resistance in subjects that possess an eligible historical genotype report. Subjects that develop virologic failure will have HIV-1 plasma genotype/phenotype of reverse transcriptase, protease and integrase.
Test Product, Dose, and Mode of Administration:	All subjects will receive elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF) FDC, administered orally, once daily, with food
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	Efficacy of switch from the current regimen to E/C/F/TAF FDC will be evaluated using HIV-1 RNA values; safety will be assessed with adverse events and clinical laboratory tests.
Safety:	Safety of E/C/F/TAF FDC will be reviewed at Weeks 12, 24 and 48 by assessing clinical laboratory tests and adverse events during the study.
Health Related Questionnaires:	Health related questionnaires will be administered, including the EQ-5D, Medical Outcome Study Short Form-36 (SF-36), Visual Analogue Scale (VAS), HIV Treatment Satisfaction Questionnaire (HIV-TSQ) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F).
Efficacy:	**Primary Endpoint:** • HIV-1 RNA < 50 copies/mL at Week 12 using pure virologic response (PVR) **Secondary Endpoints:** • Emergence of new mutations in HIV-1 reverse transcriptase and integrase (attempted on any post Day 1 sample with HIV-1 RNA ≥ 50 copies/mL) • HIV-1 RNA< 50 copies/mL at Weeks 24 and 48 using PVR • HIV-1 RNA < 50 copies/mL at Weeks 12, 24 and 48 using the FDA snapshot analysis (sensitivity analysis) • CD4+ cell count change from Day 1 at Weeks 12, 24 and 48

Statistical Methods:

The primary endpoint of pure virologic response (PVR) with HIV-1 RNA < 50 copies/mL at Week 12 will be computed.

The following criteria are considered for classifying subjects as a pure virologic responder at Week 12:

- Subject remains on study treatment
- No confirmed virologic rebound as defined by:
  - HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits
  - HIV-1 RNA ≥ 50 copies/mL during study followed by premature discontinuation

  Note: For confirmation of viral rebound, the first HIV-1 RNA must occur on or before the upper limit of the Week 12 analysis window, the confirming event (i.e., the second of the consecutive HIV-1 RNAs or premature study discontinuation) can occur after the upper limit of the Week 12 analysis window.

Subjects who meet the above criteria are pure virologic responders at Week 12; otherwise subjects are pure virologic failures (PVF) at Week 12.

Similar definition would hold for PVR at Weeks 24 and 48.

Sensitivity analyses of virologic failure will use the FDA snapshot analysis (and other sensitivity analyses such as missing equal failure) at Weeks 12, 24 and 48.

An interim efficacy analysis will be conducted when the first 50 subjects complete 12 weeks of treatment. Based on the analysis of the primary efficacy variable (HIV-1 RNA < 50 copies/mL) using pure virologic response, study conduct may be altered based on the recommendations of the internal monitoring committee.

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

The primary analysis will describe the point estimate and 95% confidence interval around the proportion of subjects with HIV-1 RNA < 50 copies/mL for the primary endpoint. If the observed pure virologic response rate is 90%, then with 100 participants, the width of the 95% CI will be ± 5.9% (large sample size approximation and binomial distribution).

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

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

DNA	deoxyribonucleic acid
DRV	darunavir
DSPH	Drug Safety and Public Health
DTG	dolutegravir
ECG	electrocardiogram
EDC	electronic data capture
ETR	Etravirine
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
E/C/F/TDF	elvitegravir (EVG) 150 mg / cobicistat (COBI) 150 mg / emtricitabine (FTC) 200 mg / tenofovir disoproxil fumarate (TDF) 300 mg single tablet regimen
E/C/F/TAF	elvitegravir (EVG) 150 mg / cobicistat (COBI) 150 mg / emtricitabine (FTC) 200 mg / tenofovir alafenamide (TAF) 10 mg single tablet regimen
ESDD	early study drug discontinuation
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FPV	Fosamprenavir
FDC	fixed dose combination
FSH	follicle-stimulating hormone
FTC	emtricitabine
F/TAF	emtricitabine/tenofovir alafenamide
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practice (Guidelines)
GFR	glomerular filtration rate
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 antibody serology
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HIV-TSQs	HIV Treatment Satisfaction Questionnaire Status
HIV-TSQc	HIV Treatment Satisfaction Questionnaire Change

HLGT	high-level group term
HLT	high-level term
HSP	hysterosalpingogram
IB	investigator's brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
INSTI	integrase strand transfer inhibitor
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
KS	Kaposi's sarcoma
LAM	Lactational amenorrhea method
LDH	lactate dehydrogenase
LLN	lower limit of the normal range
LLT	low-level term
LLOQ	lower limit of quantification
LPV	lopinavir
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
Min	minute
mmHg	millimeters mercury
MVC	maraviroc
NNRTI	non-nucleoside reverse transcriptase inhibitor
N[t]RTI	nucleos(t)ide reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
P1NP	procollagen Type 1 N-terminal propeptide
PBMCs	peripheral blood mononuclear cells
PAH	pulmonary arterial hypertension
PI	protease inhibitor
PK	pharmacokinetic
PT	preferred term
PVR	pure virologic response
PXR	pregnane-X-receptor

QA	Quality Assurance
QD	once daily
RAL	raltegravir
RBC	Red blood cells
RNA	ribonucleic acid
RPV	rilpivirine
RTV, /r	ritonavir
SA	single agent
SADR	serious adverse drug reaction
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure
SQV	Saquinavir
SSRI	selective serotonin reuptake inhibitors
STB	Stribild®, EVG/COBI/FTC/TDF (E/C/F/TDF) STR
STR	single tablet regimen
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	tenofovir alafenamide (GS-7340)
TAF fumarate	tenofovir alafenamide fumarate (GS-7340-03)
TAM	thymidine analogue-associated mutation
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate (TFVpp)
T_{max}	the time (observed time point) of C_{max}
UGT	uridine glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
VAS	visual analog scale
VR	virologic rebound
WBC	white blood cells
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the serum, plasma concentration of drug versus time curve

1. INTRODUCTION

1.1. Background

HIV-1 infection is a life-threatening and serious disease that is of major public health interest around the world. There are 35 million people worldwide and approximately 1.1 million people in the US living with HIV-1. Within Western and Central Europe, it is estimated that there are over 900,000 individuals living with HIV and 131,000 new infections in 2012.

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

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

Tenofovir disoproxil fumarate (TDF) is a preferred NRTI among recommended regimens for treatment-naïve HIV-positive patients, but is associated with nephrotoxicity and reduced bone mineral density{Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Lifelong antiretroviral treatment and the increasing comorbidities being recognized and treated in HIV-positive patients creates an urgent need to improve the safety profile of regimens that most effectively suppress HIV replication. Tenofovir alafenamide (TAF) is a novel oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription; TAF was recently added as a preferred NRTI combination by the DHHS panel {Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Gilead has coformulated TAF with the integrase strand transfer inhibitor elvitegravir (EVG), cobicistat (COBI), and emtricitabine (FTC) into a fixed dose combination (FDC). Compared to TDF, the use of TAF in the E/C/F/TAF FDC is provides enhanced lymphatic delivery of tenofovir, resulting in higher intracellular levels of the active phosphorylated moiety tenofovir-diphosphate, and lower systemic circulating levels of tenofovir. These features are translated into more F/TAF effective suppression of viral replication, and an improved tolerability and safety profile, especially with respect to renal and bone safety.

The prevalence of M184V resistance mutation in reverse transcriptase (RT) region in HIV-1-infected pretreated patients is high {Miller et al 2004}, {Riddler et al 2008}, {Blanco et al 2014}, {Poon et al 2011}, {Haubrich et al 2007b}. In addition, patients with virologic failure to the first NNRT-based regimen will develop the M184V mutation in up to 60% of cases {Riddler et al 2008}, {Marconi et al 2008}, {Saini et al 2012}, {Miller et al 2012}. This mutation confers resistance to both FTC and 3TC, but not to tenofovir. However FTC may provide some benefit on viruses harboring M184V through the reduced viral fitness associated with this mutation {Wei et al 2002}, {Wei et al 2003}, {Deval et al 2004}. The M184V mutation also sensitizes the viral strain to TFV; viral hypersensitivity has been associated with better virologic response to regimens that contain the hypersensitive drug {Haubrich et al 2002}, {Whitcomb et al 2002}, {Shulman et al 2001}, {Haubrich 2004}, {Haubrich et al 2007a}.

The presence of HIV drug resistance mutations prior to treatment (i.e., transmitted drug resistance) may affect virologic outcome if the mutation reduces susceptibility to a drug in the regimen. Reduced outcome with transmitted resistance has been best demonstrated for the NNRTI and INSTI based regimens {Gibson et al 2014}, {Nicot et al 2015}, {Callegaro et al 2014}, {Li et al 2013a}, {Li et al 2013b}. However, some mutations, even in the same drug class, may not preclude viral suppression. In an integrated resistance analysis from the phase 3 E/C/F/TDF treatment naïve studies, Kulkarni reported that 25% (89/353) had a baseline mutation, with 9% of subjects having an NRTI mutation (including TAMs), 2% having PI mutations and 17% having an NNRTI mutation {Kulkarni et al 2014}. Subjects with preexisting drug resistance mutations achieved Week 144 HIV-1 RNA < 50 copies/mL at rates similar to those without mutation (76% versus 78%, respectively).

To date, switch options in patients harboring isolated NRTI M184V/I mutation are limited. PI/r + FTC/TDF is currently the preferred choice. Continuing a PIr-based regimen raises the problem of long-term tolerability and cardiovascular risk in an aging population. Furthermore existing antiretroviral therapies used in this population have a high pill burden. Patients harboring M184V/I resistance mutation cannot benefit from a switch to TDF-based FDCs (EFV/FTC/TDF, RPV/FTC/TDF or EVG/COBI/FTC/TDF) because such patients were excluded from switch studies with these FDCs. Switching from a PI/r to an NNRTI-based regimen, which theoretically has a lower barrier to resistance, has been successful with RPV/TDF/FTC in the SPIRIT study {Palella et al 2014}. Of 23 subjects with baseline NNRTI resistance (K103N), 22/24 (92%) maintained viral suppression at the last follow-up visit. Thus, there is precedent to switching from a PI/r regimen to a regimen without a PI with continued excellent control of viral suppression.

In addition, 4 subjects randomized to receive E/C/F/TDF in the Strategy-PI and Strategy-NNRTI protocols that had M184V mutations at baseline (mutations that were prohibited by protocol entry criteria and discovered during treatment) achieved viral suppression:

- **Subject 1:** M184V, discontinued at Week 4 by medical monitor, HIV RNA < 50 copies/mL
- **Subject 2:** M41L+L210W+T215Y, discontinued at Week 12 by the medical monitor, HIV RNA < 50 copies/mL

- **Subject 3:** M184V, discontinued at Week 24, HIV RNA < 50 copies/mL
- **Subject 4:** M184V, stayed on study to Week 96, HIV RNA < 50 copies/mL

TAF is a novel prodrug of tenofovir with a unique metabolism that provides enhanced lymphoid cells delivery of tenofovir, resulting in a 4 fold increase in intracellular TFV-DP in PBMCs. Potentially, these higher intracellular levels of TFV-DP delivered by TAF may allow this agent to overcome resistance mutations that might decrease TDF potency. In vitro, TAF activity is observed to be better than TDF against NRTI resistant viruses (K65R, multiple TAMs and/or M184V) {Margot et al 2013}. In patients with limited treatment options because of an isolated M184V, E/C/F/TAF could be an option for simplification and could offer an alternative for those who cannot tolerate PI/r or who are at high cardiovascular risk.

1.2. Tenofovir Alafenamide (TAF, GS-7340)

1.2.1. General Information

Tenofovir alafenamide (GS-7340, TAF, or L-Alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]/phenoxyphosphinyl]-, 1-methylethyl ester) is a second generation oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP), a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the elongation of the viral DNA chain. In the development of TAF, three forms of the drug substance have been used in various studies: GS-7340, synonym for GS-7340 as the free base; GS-7340-02, synonym for TAF monofumarate (1:1); and GS-7340-03 as the hemifumarate (2:1). GS-7340-03, also known as TAF fumarate, is considered comparable, based on physical/chemical properties, to GS-7340-02 that has been used in previous studies and a number of ongoing studies. GS-7340-03 was also used in the Phase 2 study GS-US-292-0102 and several Phase 3 studies (for example: GS-US-292-0104 and GS-US-292-0111). GS-7340-03 and GS-7340-02 exist as the free base, TAF (GS-7340), in blood and biological fluids.

For further information, refer to the current Investigator's Brochure for E/C/F/TAF.

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. Primary Pharmacodynamics

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

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

1.2.2.2. Safety Pharmacology

TAF monofumarate (GS-7430-02) has been evaluated to determine potential effects on the central nervous system (R990188), renal system (R990186), cardiovascular (D2000006) and gastrointestinal systems (R990187). Single doses did not induce pharmacologic effects on the central nervous system of the rat (1000 mg/kg), the renal system of the rat (1000 mg/kg), or the cardiovascular system of the dog (100 mg/kg). TAF monofumarate (at 1000 mg/kg reduced distal transit and increased stomach weights starting 2 hours post-dosing with reversibility beginning by 6 hours after dosing. The NOEL for gastrointestinal motility was 100 mg/kg. The IC_{50} for the inhibitory effect of TAF fumarate (GS-7340-03) on hERG potassium current was estimated to be greater than 10 μM.

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

Plasma pharmacokinetics of the intact prodrug, TAF, following oral administration of GS-7340-02 in dogs and monkeys demonstrated rapid absorption with peak plasma concentrations between 0.25 and 0.5 hours. Peak TFV plasma concentrations occurred following TAF absorption, with TFV T_{max} values between 0.25 to 1.7 hours in rats, dogs, and monkeys. TFV plasma concentrations declined with a terminal half-life of 11.2 to 16.4 hours in rats (fasted), > 24 hours in dogs (fasted) and 8.1 to 12.5 hours in rhesus monkeys.

The tissue distribution and recovery of [14C] radiolabeled GS-7340-02 was examined in beagle dogs. Radioactivity was detected in all tissues except brain, with the majority present in the contents of the gastrointestinal tract, liver, kidney, and large intestine. Tissue concentrations were the highest in kidney, PBMCs, liver, large intestine, and bile. Significant concentrations of TFV-related radioactive material were observed in lymph nodes suggesting that TAF may be selectively cleaved to tenofovir in the cells of the lymphoreticular system. The primary route of elimination of tenofovir is renal excretion of unchanged drug based on IV studies of tenofovir. Following oral administration of GS-7340-02, approximately 15% of a radiolabeled dose is recovered in dog urine in 24 hrs. Tenofovir was the major species present in the urine (90%), with about 3.4% of TAF also present. Biliary excretion of tenofovir in dogs and fecal elimination of tenofovir in rats and dogs are negligible.

Tenofovir was the only species found in the intestinal contents and feces. In human systems, TAF is metabolized by hydrolytic cleavage and, to a lesser extent, by CYP3A4 catalyzed oxidation (AD-120-2004). As a result of the limited metabolism of TAF by CYP3A4 inhibition or induction of this enzyme should have little consequence on TAF exposure in vivo. TAF has

limited potential to alter CYP enzyme activity through inhibition and does not inhibit UGT1A1 function. In addition, TAF is not an activator of either the aryl hydrocarbon receptor (AhR) or human pregnane-X-receptor (PXR). These features combined with the relatively low plasma exposures of TAF in humans suggest that the potential of TAF to cause or be affected by clinically relevant drug-drug interactions is very low.

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

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

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

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

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

- **Studies GS-US-292-0104 and GS-US-292-0111** are two Phase 3, controlled, double-blind studies evaluating treatment-naive HIV-infected patients. These patients were recruited with an estimated creatinine clearance of 50 mL per min or higher from 178 outpatient centers in 16 countries. Patients were randomly assigned (1:1) to receive E/C/F/TAF or E/C/F/TDF with matching placebo. Randomization was done by a computer-generated allocation sequence (block size 4) and was stratified by HIV-1 RNA, CD4 count, and region (USA or ex-USA). Investigators, patients, study staff, and those assessing outcomes were masked to treatment group. All participants who received one dose of study drug were included in the primary intention-to-treat efficacy and safety analyses. The main outcomes

were the proportion of patients with plasma HIV-1 RNA less than 50 copies per mL at Week 48 as defined by the US Food and Drug Administration (FDA) snapshot algorithm (pre-specified non-inferiority margin of 12%) and pre-specified renal and bone endpoints at 48 weeks. There were 1733 patients who received treatment (866 given E/C/F/TAF and 867 given E/C/F/TDF). E/C/F/TAF was non-inferior to E/C/F/TDF, with 800 (92%) of 866 patients in the TAF group and 784 (90%) of 867 patients in the TDF group having plasma HIV-1 RNA less than 50 copies per mL (adjusted difference 2.0%, 95% CI -0.7 to 4.7). Patients given E/C/F/TAF had significantly smaller mean serum creatinine increases than those given E/C/F/TDF (0.08 vs 0.12 mg/dL; $p < 0.0001$), significantly less proteinuria (median % change -3 vs 20; $p < 0.0001$), and a significantly smaller decrease in bone mineral density at spine (mean % change -1.30 vs -2.86; $p < 0.0001$) and hip (-0.66 vs -2.95; $p < 0.0001$) at 48 weeks. Interpretation through 48 weeks, more than 90% of patients given E/C/F/TAF or E/C/F/TDF had virologic success. Renal and bone effects were significantly reduced in patients given E/C/F/TAF.

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

- **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.

1.3. Information About Comparator Regimens

There are no comparator regimens in this study; all subjects will be switched to E/C/F/TAF.

1.4. Rationale for this Study

The aim of this pilot study is to validate the ability of E/C/F/TAF to maintain virological suppression in patients harboring M184V and/or M184I isolated mutations to NRTIs when switching from a TDF- or ABC-based regimen.

1.5. Risk/Benefit Assessment for the Study

Potential risks of a patient's study involvement include switching to a new unfamiliar regimen with potential loss of virologic control due to underlying HIV-1 drug resistance, the inconvenience of more frequent clinical study visits and laboratory blood draws, and the associated pain and discomfort of phlebotomy. Risk will be mitigated by careful monitoring for virologic failures in real time during the conduct of the study and review by an internal data monitoring committee. Potential benefits may include the patient receiving a new antiretroviral regimen that is more convenient leading to improved adherence, potentially fewer adverse events than the current regimen, gaining access to E/C/F/TAF when it is not widely available or currently covered by the payer/healthcare system, and the knowledge that patient participation will be contributing towards a body of science.

1.6. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the efficacy of E/C/F/TAF fixed dose combination (FDC) after switching from a stable regimen consisting of FTC/TDF or ABC/3TC plus a third antiretroviral agent in maintaining HIV-1 RNA < 50 copies/mL at Week 12 (using pure virologic response) in subjects harboring the archived NRTI resistance mutation M184V and/or M184I in HIV-1 reverse transcriptase

The secondary objectives of this study are:

- To determine the safety and tolerability of E/C/F/TAF FDC in subjects switching from 2 NRTI plus third antiretroviral agent regimens

- To evaluate the development of new resistance mutations in subjects who develop virologic failure after switching to E/C/F/TAF FDC

- To determine the durability of efficacy at Weeks 24 and 48 in maintaining HIV-1 RNA < 50 copies/mL using pure virologic response (PVR)

3. STUDY DESIGN

3.1. Study Design

This protocol describes an open-label, single arm, multicenter, two part study to evaluate the efficacy and safety of switching to E/C/F/TAF FDC in HIV-1 infected adult subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) harboring an archived isolated M184V and/or M184I mutation and who have been on a stable regimen consisting of FTC/TDF or ABC/3TC plus a third antiretroviral agent for ≥ 6 consecutive months prior to screening.

Both Part 1 and Part 2 will consist of subjects who have a documented presence of M184V and/or M184I mutations (mixtures are acceptable) in reverse transcriptase.

In Part 1, the first 50 subjects will have M184V and/or M184I (mixtures are acceptable) in reverse transcriptase WITHOUT any other NRTI resistance mutation (including thymidine analogue-associated mutations (TAMs) [M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R], K65R, K70E, T69 insertion, and/or Q151M mutation complex [A62V, V75I, F77L, F116Y, Q151M]. See Table 3-1.

If the rate of virologic failure in Part 1 is deemed acceptable, once the internal DMC officially completes the interim review the study will continue to Part 2 (with the expanded entry criteria).

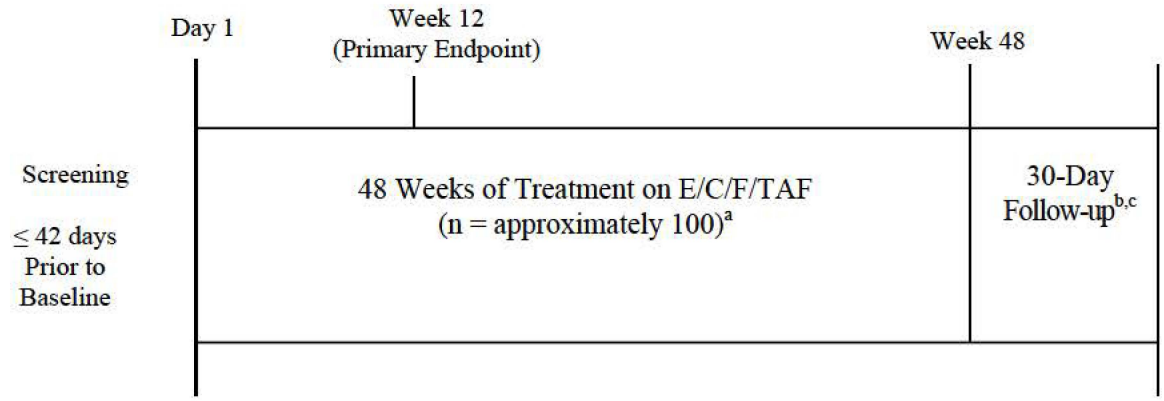
In Part 2, the second 50 subjects will have M184V and/or M184I (mixtures are acceptable) in reverse transcriptase WITH or WITHOUT 1 or 2 thymidine analog-associated mutations. Evidence of K65R, K70E,T69 insertion, and/or Q151M mutation complex in subjects in addition to the resistance mutations above will not be eligible for entry into the study. See Table 3-1.

Table 3-1. Part 1 and Part 2 Resistance Criteria

	Part 1	Part 2
Inclusion Resistance Mutations		
TAMs	0 from:	0, 1, or 2 from:
	M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R	
Exclusion Resistance Mutations		
NRTI-R	Any from: K65R, K70E,T69 insertion, Q151M mutation complex [A62V, V75I, F77L, F116Y, Q151M]	
Primary PI-R	Any	
Primary INSTI-R	Any	
Additional Allowed Resistance Mutations		
NRTI-R	Any not defined above	
NNRTI-R	Any	

TAM = thymidine analogue-associated mutation; NRTI = nucleos(t)ide reverse transcriptase inhibitor; PI = protease inhibitor; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; -R = resistance

Figure 3-1. Study Schema



a Following the Day 1 visit, subjects will return for study visits at Weeks 4, 8, 12, 16, 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 switch from their current regimen consisting of FTC/TDF or ABC/3TC plus a third antiretroviral agent to E/C/F/TAF FDC on Day 1.

Allowed third agents include LPV/r, ATV+RTV, ATV+COBI, DRV+RTV, DRV+COBI, FPV + RTV, SQV + RTV, ATV(no booster) EFV, RPV, NVP, ETR, RAL or DTG. See Table 4-1.

3.3. Duration of Treatment

The study will consist of a 42-day screening period (within 42 days before Day 1 visit), followed by a 48 week treatment period. After Day 1, subjects will return for study visits at Weeks 4, 8, 12, 16, 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 study is defined as completion of the 48 weeks of treatment and the 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

Gilead will provide source document worksheets for all study visits.

3.7. Samples for Optional Exploratory Assessments

CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 100 subjects who meet the eligibility criteria will be enrolled.

4.2. Inclusion Criteria

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

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

2) Age ≥ 18 years

3) Documented historical genotype report showing M184V and/or M184I (mixtures are acceptable) in reverse transcriptase. Subjects must not have any primary INSTI or primary PI resistance mutations present on historical genotype; NNRTI mutations are allowed.

   Proviral DNA test must not have additional exclusion resistance mutations against PIs, NRTIs and INSTIs. See Table 3-1.

   - **Part 1 (first 50 subjects):** Historical genotype report must show M184V and/or M184I in reverse transcriptase WITHOUT any other NRTI resistance mutation (including thymidine analogue-associated mutations (TAMs) [M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R], K65R, K70E, T69 insertion and Q151M mutation complex [A62V, V75I, F77L, F116Y, Q151M]). See Table 3-1.

   - **Part 2 (after the interim efficacy review – 50 subjects):** Historical genotype report must show M184V and/or M184I in reverse transcriptase WITH or WITHOUT one or two thymidine analogue-associated mutations (TAMs) [M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R]. Evidence of K65R, K70E, T69 insertion and/or Q151M mutation complex [A62V, V75I, F77L, F116Y, Q151M] will not be eligible. See Table 3-1.

4) Currently receiving an antiretroviral regimen consisting of FTC/TDF or ABC/3TC in combination with one third antiretroviral agent for ≥ 6 consecutive months preceding the Screening Visit. Refer to Table 4-1 for allowed third agents of the pre-existing regimen

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

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

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

6) Plasma HIV-1 RNA levels < 50 copies/mL at Screening Visit

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

8) Estimated glomerular filtration rate ≥ 30 mL/min according to the Cockcroft-Gault formula for creatinine clearance ($eGFR_{CG}$) {Cockcroft et al 1976}:

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

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

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

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

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

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

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

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

   c) 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.

d) Of childbearing potential and agrees to utilize the protocol specified method of contraception or be non-heterosexually active or practice sexual abstinence from screening throughout the duration of study treatment and for 30 days following discontinuation of study drugs (as defined in Appendix 5)

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

13) Male subjects must agree to use the protocol specified method(s) of contraception during heterosexual intercourse or be non-heterosexually active, or practice sexual abstinence from screening throughout the study period and for 30 days following the last study drug dose.

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

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

Antiretroviral Class	Agents
Boosted PI	LPV/r[a], ATV+RTV[a], ATV+COBI[a] (or ATV/COBI[a] FDC), DRV+RTV[a], DRV+COBI[a] (or DRV/COBI[a] FDC) FPV+RTV, SQV+RTV, ATV(no booster)
NNRTI	EFV, RPV, NVP, ETR
INSTI	RAL, DTG

a Change of pharmacoenhancer between RTV and COBI in itself, including change from PI+RTV to PI/COBI, is not considered as change of regimen.

4.3. Exclusion Criteria

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

14) Subjects will have no evidence of previous virologic failure on a PI/r or INSTI-based regimen (with or without resistance to either class of ART). Subjects may have evidence of prior virologic failure on only an NNRTI plus 2 NRTI-based regimen.

15) Subjects on a current PI/r-based regimen will have no evidence of previous use of any approved or experimental integrase strand transfer inhibitor (INSTI) (for any length of time).

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

17) Hepatitis C infection that would require therapy during the study

18) Hepatitis B surface antigen (HBsAg) positive

19) Subjects with clinical evidence of decompensated cirrhosis (e.g., ascites, encephalopathy, variceal bleeding, etc.)

20) Females who are breastfeeding

21) Positive serum pregnancy test

22) Have an implanted defibrillator or pacemaker

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

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

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

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

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

28) Subjects receiving ongoing therapy with any of the medications in Table 4-2 and those listed in Section 5.4, including drugs not to be used with EVG, COBI, FTC or TAF (For EVG, COBI, and FTC refer to the individual agents Prescribing Information; for TAF refer to the E/C/F/TAF FDC Investigator's Brochure); or subjects with any known allergies to the excipients of E/C/F/TAF FDC tablets.

Table 4-2. Disallowed Agents

Drug Class	Agents Disallowed[a]
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

a 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 subjects will receive open-label E/C/F/TAF.

Subjects will be assigned a screening number at the time of consent. Investigators must consult with the Medical Monitor and receive written approval prior to re-screening subjects.

Prior to enrollment to Day 1, the historical genotype report and proviral DNA resistance test result must be reviewed and approved by Gilead and subject eligibility confirmed.

Once eligibility has been confirmed by Gilead, each subject will be assigned a unique subject number using an Interactive Web Response System (IWRS). Once a subject number has been assigned, it will not be reassigned to any other subject. The subject number assignment 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.

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

The IWRS will assign open-label study drug bottle numbers at each study visit. Study drug will be dispensed to the subjects in an open-label fashion. Initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit.

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

5.2.1. Formulation

E/C/F/TAF FDC tablets are capsule-shaped, film-coated green tablets and are debossed with "GSI" on one side of the tablet and "510" on the other side of the tablet. E/C/F/TAF tablets contain 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF (as 11.2 mg of TAF fumarate). The E/C/F/TAF tablet core contains silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate as inactive ingredients and are film-coated with indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

5.2.2. Packaging and Labeling

E/C/F/TAF FDC tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in participating countries shall be labeled to meet applicable requirements of the 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 drugs should be stored in a securely locked area, accessible only to authorized site personnel.

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

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

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

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

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.

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

5.4. Prior and Concomitant Medications

- Subjects receiving hormonal contraceptives 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.
- Subjects receiving concomitant medications that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious adverse events 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 (e.g., 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).

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
Antihistamines	Astemizole, Terfenadine	
Antimycobacterials	Rifampin, Rifapentine, Rifabutin	
β-Blockers		Metoprolol, Timolol: Clinical and ECG monitoring of subjects is recommended. A dose decrease may be needed.
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 (e.g., 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)	Pulmonary Arterial Hypertension: Tadalafil: Caution should be exercised, including consideration of dose reduction, when coadministered for treatment of pulmonary arterial hypertension. Erectile Dysfunction: 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 of Study Drug

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 medication 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 for return. If return is not possible, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead Quality Assurance (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 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 bottles and associated records at periodic intervals.

6. STUDY PROCEDURES

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

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

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that the subject is eligible prior to enrollment.

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

- Obtain written informed consent
- Obtain medical history, including history of HIV-1 disease-related events, cigarette smoking (current or previous smoker), diabetes, family cardiovascular history 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)
- Height and weight
- 12-lead ECG performed supine
- Urine collection for the following laboratory analyses:
  - Urinalysis and Urine chemistry

- Blood sample collection for the following laboratory analyses:
  - Serum pregnancy test (females of childbearing potential only). If the test is positive, the subject will not be enrolled.
  - FSH test is required for female subjects (age > 54 years) who have stopped menstruating for > 12 months but do not have documentation of ovarian hormonal failure.
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium and sodium
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula ($eGFR_{CG}$){Cockcroft et al 1976}:

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

    Female: $\frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})} = CL_{cr}$ (mL/min)
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - CD4+ cell count
  - Plasma HIV-1 RNA
  - Hepatitis B virus surface antigen serology (HBsAg)
  - Hepatitis C virus (HCVAb) serology (reflex HCV RNA is performed in subjects with positive HCVAb serology)
  - Whole blood sample collection for proviral genotype analysis of archived resistance
- Review of concomitant medications
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 42 days after screening for the 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 electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Day 1 Visit

Eligible historical genotype report and subsequent proviral genotype test result for archived resistance must both be reviewed and approved by Gilead to confirm subject eligibility. Once subject's full eligibility is confirmed, the following evaluations are to be completed at the Day 1 Visit. The subject must complete all Day 1 assessments before being dispensed the study drug. Initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit.

- 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), including weight
- Urine collection for the following laboratory procedures:
  - Urinalysis and urine chemistry
  - Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive at Day 1 visit, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will not be able to participate.
  - Urine sample storage for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium and sodium
  - Cystatin C testing
  - 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 GFR, according to the Cockcroft-Gault formula for creatinine clearance
  - Hematology profile: CBC with differential and platelet count
  - Plasma HIV-1 RNA

- CD4+ cell count
- Plasma sample storage for safety and virology testing
- CCI [redacted]

- Questionnaires: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.
  - Visual Analog Scale (VAS)
  - HIV Treatment Satisfaction Questionnaire Status (HIV-TSQs)
  - EQ-5D
  - Medical Outcome Study Short Form-36 (SF-36)
  - Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)
- Study drug dispensation. Study drug will be dispensed in an open-label fashion. Subjects must initiate dosing of study drug within 24 hours after 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. Subjects should also be counseled regarding the importance of adherence and taking their study medications at approximately the same time each day.

6.3. Treatment Assessments

6.3.1. Treatment Visits (Weeks 4 – 48)

The following evaluations are to be completed at the end of Weeks 4, 8, 12, 16, 24, 36 and 48 unless otherwise specified.

All study visits are to be scheduled relative to the Day 1 visit date. Study visits are to be completed within ± 2 days of the protocol-specified visit date through Week 16 and completed within ± 6 days of the protocol-specified visit date through Week 36, unless otherwise specified. The visit window at Week 48 will be ± 6 weeks of the protocol-specified visit date, which coincides with the Week 48 statistical analysis window for HIV-1 RNA. For the purposes of scheduling the Week 48 visit, a ± 6 day window of the protocol-specified visit date should be used.

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

Note: At the Week 16 visit, the only assessments to be completed are:

- Review of AEs and changes in concomitant medications
- Blood sample collection for the following laboratory analyses:
  - Plasma HIV-1 RNA
  - Plasma sample storage for safety and virology testing
- Document study drug dispensation and accountability for all study drug dispensed.
- Questionnaire: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.
  - Visual Analog Scale (VAS)

For all other visits, please complete the following:

- Review of AEs and changes in concomitant medications
- Complete physical examination (**Weeks 24 and 48**) (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Symptom-directed physical examination as needed (**Weeks 4, 8, 12 and 36**)
- 12-lead ECG performed supine (**Week 48 only**)
- Vital signs (blood pressure, pulse, respiration rate, and temperature), including weight
- Urine collection for the following laboratory procedures:
  - Urinalysis and urine chemistry
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be discontinued.
  - Urine sample storage for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium and sodium. **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**.

  - 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**).
  - Estimated GFR, according to the Cockcroft-Gault formula for creatinine clearance
  - Hematology profile: CBC with differential and platelet count
  - Plasma HIV-1 RNA
  - CD4+ cell count
  - Plasma sample storage for safety and virology testing
  - CCI [redacted]

- Subjects who meet the criteria for virologic rebound should be managed according to Management of Virologic Failure (Section 6.8).
- HIV-1 geno/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 50 copies/mL (**Week 48 only**)
- Questionnaires: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.
  - Visual Analog Scale (VAS) (**Weeks 4, 8, 12, 24, 36 and 48**)
  - HIV Treatment Satisfaction Questionnaire Change (HIV-TSQc) (**Weeks 4, 24, and 48**)
  - EQ-5D (**Weeks 24 and 48**)
  - SF-36 (**Weeks 24 and 48**)
  - FACIT-F (**Weeks 24 and 48**)
- Document study drug dispensation (**Weeks 4, 8, 12, 24, and 36**) and accountability for all study drug dispensed.

6.4. Post-treatment Assessments

6.4.1. Early Study Drug Discontinuation (ESDD) Visit

If a 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. The subject will be asked to continue attending the scheduled study visits through Week 48.

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

The following evaluations are to be completed at 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), including weight
- Urine collection for the following laboratory procedures:
  - Urinalysis and urine chemistry
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test.
  - Urine sample storage for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium and sodium
  - Estimated GFR, according to the Cockcroft-Gault formula for creatinine clearance
  - Hematology profile: CBC with differential and platelet count
  - Plasma HIV-1 RNA
  - CD4+ cell count
  - Plasma sample storage for safety and virology testing
  - CCI [redacted]

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

  — Visual Analog Scale (VAS)

  — HIV-TSQc

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

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

  — HIV Treatment Satisfaction Questionnaire Change (HIV-TSQc)

- Study drug accountability

6.4.2. 30-Day Follow-up Visit

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

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

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

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

- Review of AEs and changes in concomitant medications

- Symptom-directed physical examination as needed

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

- Urine collection for the following laboratory procedures:

  — Urinalysis and urine chemistry

- Blood sample collection for the following laboratory analyses:

  — Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium and sodium

— Hematology profile: CBC with differential and platelet count

— Plasma HIV-1 RNA

— CD4+ cell count

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

6.5. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study (see Section 6.6, Criteria for Discontinuation of Study Treatment) and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study.

6.6. Criteria for Discontinuation of Study Treatment

Study drug may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Lack of efficacy (virologic failure)
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 5
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.7. Other Evaluations

6.7.1. Blood and Urine Storage

CCI [redacted]

6.8. Virologic Failure

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

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

6.8.1. 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)
- Investigators should discuss the management of all subjects with confirmed virologic failure with the Medical Monitor.
- If virologic failure is confirmed at the scheduled or unscheduled visit and HIV-1 RNA is ≥ 50 copies/mL, the blood samples from the confirmation visit will be used for HIV-1 genotype/phenotype testing.

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

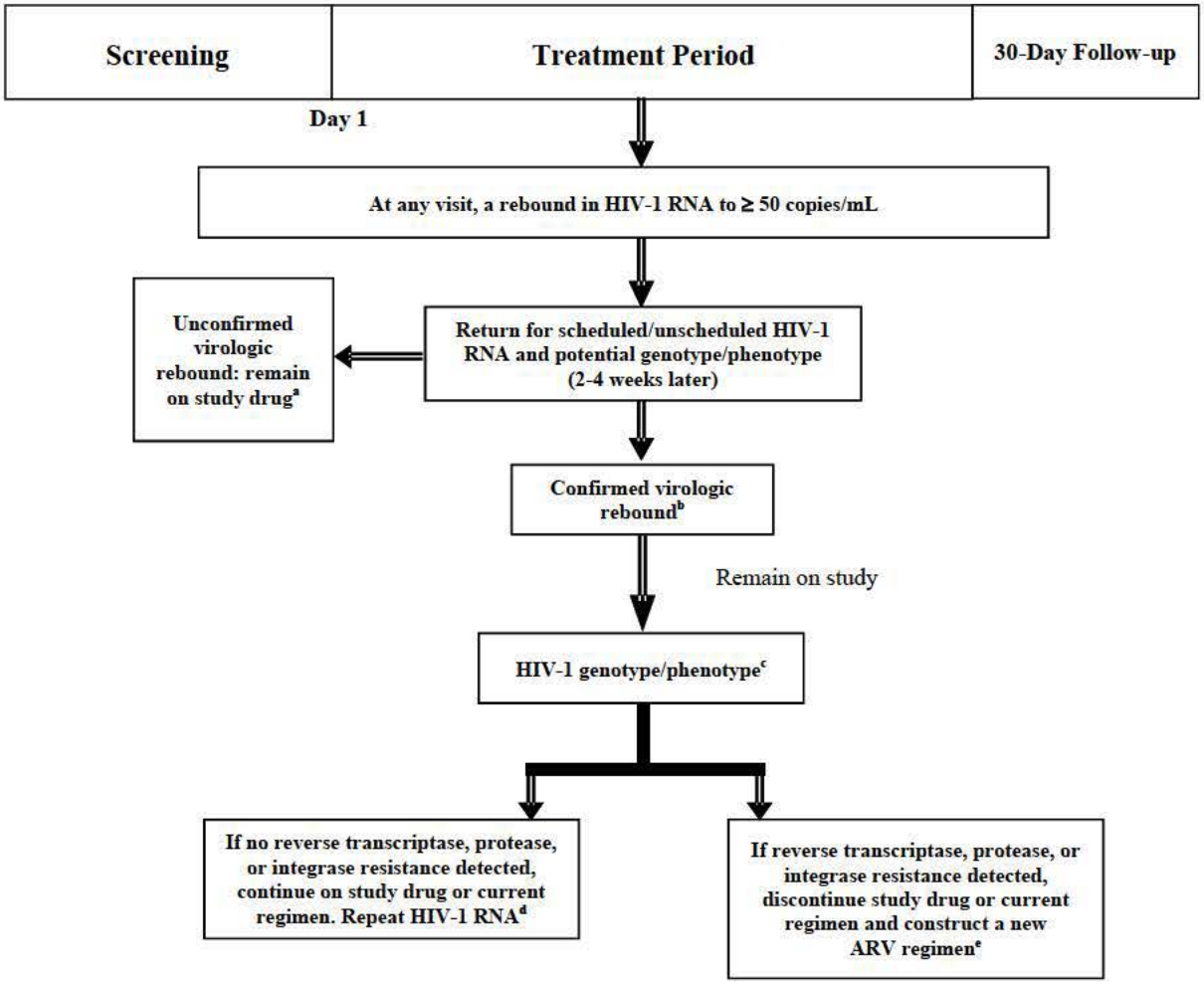
- If no resistance is detected from genotype/phenotype testing, subject may remain on study drug and a repeat HIV-1 RNA should be repeated (2-4 weeks from the date of confirmed test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug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

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

6.8.2. Resistance Analysis at Subjects Last Visit

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

Figure 6-1. Management of Virologic Failure



a If virologic rebound is not confirmed, the subject will remain on the study drug.
b If virologic rebound is confirmed, and the HIV-1 RNA is ≥ 50 copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase resistance) will be analyzed.
c Based on the results of the genotype/phenotype assays, the subject will remain or discontinue study drug. If genotyping/phenotyping assay fails, a new ARV regimen may be configured at the discretion of the Investigator in consultation with the Medical Monitor.
d If no resistance detected, HIV-1 RNA will be repeated (2-4 weeks later). Investigator reviews study drug continuation/discontinuation options and discusses with Medical Monitor prior to discontinuation.
e A new ARV regimen will be configured, at the Investigator's discretion, and the subject will remain in the study.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1*)*
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history 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 Appendix 3.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No:** Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (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 study drug.

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

The relationship to study procedures (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 4). For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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

Requirements for Collection Prior to Study Drug Initiation

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

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

Adverse Events

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

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

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (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 CRF/eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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

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

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

- At the time of study start, SAEs will be reported using an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

Electronic Serious Adverse Event (eSAE) Reporting Process

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

- If for any reason it is not possible to record the SAE information electronically, i.e., the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours as described below.

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

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

- 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.

- 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 only 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 CRF/eCRF and the event description section of the SAE form.

Serious Adverse Event Paper Reporting Process

- All SAEs will be recorded on the serious adverse event report form and submitted by faxing or emailing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead DSPH or to the designated CRO.

Gilead Sciences DSPH	Fax:	PPD
	E-mail:	PPD

7.4. Gilead Reporting Requirements

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

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

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

7.5. Toxicity Management

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

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

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

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

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue study drug at the discretion of the Investigator.

7.5.2. Grade 3 Laboratory Abnormality or Clinical Event

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

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

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

7.5.3. Grade 4 Laboratory Abnormality or Clinical Event

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

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

7.5.4. Management of Potential Nephrotoxicity

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

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

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

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

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

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, occupational exposure with an AE, AEs in infants that occur while breastfeeding,and pregnancy reports regardless of an associated AE.

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

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

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

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

Product complaint associated with an adverse event is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product associated with an adverse event, which is any untoward medical occurrence in a study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the study drug.

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. 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. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows:
Email: PPD and Fax: PPD .

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

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

7.6.2.2. 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 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.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate the efficacy of E/C/F/TAF fixed dose combination (FDC) after switching from a stable regimen consisting of FTC/TDF or ABC/3TC plus a third antiretroviral agent in maintaining HIV-1 RNA < 50 copies/mL at Week 12 (using pure virologic response) in subjects harboring the archived NRTI resistance mutation M184V and/or M184I in HIV-1 reverse transcriptase

The secondary objectives of this study are as follows:

- To determine the safety and tolerability of E/C/F/TAF FDC in subjects switching from 2 NRTI plus third antiretroviral agent regimens

- To evaluate the development of new resistance mutations in subjects who develop virologic failure after switching to E/C/F/TAF FDC

- To determine the durability of efficacy at Weeks 24 and 48 in maintaining HIV-1 RNA < 50 copies/mL using pure virologic response (PVR)

8.1.2. Primary Endpoint

The primary endpoint is the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 12 as defined by pure virologic response.

8.1.3. Secondary Endpoint

The secondary endpoints are the proportion of subjects with:

- Emergence of new mutations in HIV-1 reverse transcriptase and integrase (attempted on any post Day 1 sample with HIV-1 RNA ≥ 50 copies/mL)

- HIV-1 RNA< 50 copies/mL at Weeks 24 and 48 using PVR

- HIV-1 RNA < 50 copies/mL at Weeks 12, 24 and 48 using the FDA snapshot analysis (sensitivity analysis)

- CD4+ cell count change from Day 1 at Weeks 12, 24 and 48

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

8.2.1.1.1. Full Analysis Set (FAS)

The Full Analysis Set will include all the subjects who were randomized and received at least one dose of study drug. The FAS will exclude subjects with major protocol violations (e.g., not having the correct historical mutation at study entry). The FAS analysis set is the primary analysis set for the efficacy analyses.

8.2.1.2. Safety

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.

8.3. Demographic Data and Baseline Characteristics

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

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

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

8.4. Efficacy Analysis

8.4.1. Primary Analysis

The primary endpoint of pure virologic response (PVR) with HIV-1 RNA < 50 copies/mL at Week 12 will be computed.

The following criteria are considered for classifying subjects as a pure virologic responder at Week 12:

- Subject remains on study treatment
- No confirmed rebound as defined by:
  - HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits;
  - HIV RNA ≥ 50 copies/mL during study followed by premature discontinuation of study

  Note: For confirmation of viral rebound, the first HIV-1 RNA must occur on or before the upper limit of the Week 12 analysis window, the confirming event (i.e., the second of the consecutive HIV-1 RNAs or premature study discontinuation) can occur after the upper limit of the Week 12 analysis window.

Subjects who meet the above criteria are pure virologic responders at Week 12; otherwise subjects are pure virologic failures (PVF) at Week 12. The 95% CI will be computed using normal approximation to the binomial proportions of PVR

8.4.2. Secondary Analyses

A similar definition to the primary endpoint will be used for computing PVR at Weeks 24 and 48.

Sensitivity analyses of virologic failure using the FDA snapshot algorithm at Weeks 12, 24 and 48 (and other sensitivity analyses such as missing equal failure) will also be conducted.

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 dispensed up to the date of last dose of study drug plus 30 days will be summarized. Data for the pretreatment 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 4).

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to the date of last dose of study drug plus 30 days, will be summarized. 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. Sample Size

The primary analysis will describe the point estimate and 95% confidence interval around the proportion of subjects with HIV-1 RNA < 50 copies/ mL for the primary endpoint. If the observed pure virologic response rate is 90%, then with 100 participants, the width of the 95% CI will be ± 5.9% (large sample size approximation and binomial distribution).

8.7. Data Monitoring Committee

An internal data monitoring committee (Internal DMC), independent of the study team, will review the progress of the study and perform interim reviews of safety, efficacy data and provide recommendation to Gilead whether the efficacy and 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 50 subjects enrolled complete Week 12 of the study. Based on the analysis of the primary efficacy variable (HIV-1 RNA < 50 copies/mL) using pure virologic response, study conduct may be altered based on the recommendations of the internal monitoring committee.

The Internal DMC's specific activities will be defined by a mutually agreed charter, which will define the Internal DMC'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, "Protection of Human Subjects", and 21 CFR, Part 56, "Institutional Review Boards".

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

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

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

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.
The investigator must use the most current IRB/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 documented according to study procedures. The eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Inspections

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

9.1.8. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3b Open-Label Pilot Study to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed Dose Combination (FDC) in Virologically-Suppressed HIV-1 Infected Adult Subjects Harboring the Archived Isolated NRTI Resistance Mutation M184V/M184I

GS-US-292-1824, Amendment 1, 19 August 2016

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

PPD

Medical Monitor

PPD

Signature

8/19/2016

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

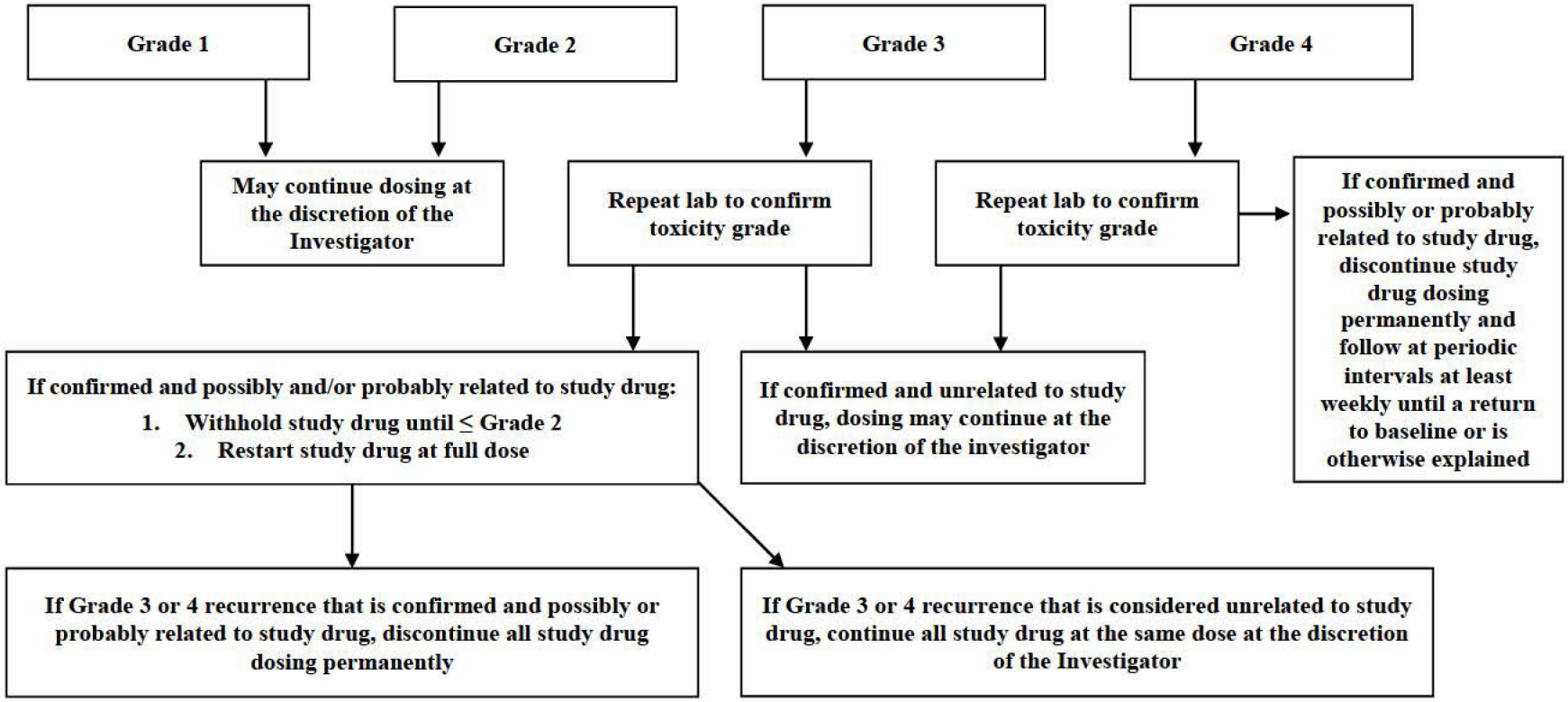
Appendix 2. Study Procedures Table

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]							30 Day Follow-up	ESDD[d]
			4	8	12	16[t]	24	36	48		
Informed Consent	X										
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam[e]	X	X					X		X		X
Symptom-Directed Physical Exam[f]			X	X	X			X		X	
12-Lead ECG (Performed Supine)	X								X		X
Vital Signs and Weight	X	X	X	X	X		X	X	X	X	X
Height	X										
Urinalysis and Urine Chemistry	X	X	X	X	X		X	X	X	X	X
Urine Storage Sample		X	X	X	X		X	X	X		X
Urine Pregnancy Test[g]		X	X	X	X		X	X	X		X
Serum Pregnancy Test[g]	X										
Chemistry Profile[h]	X	X	X	X	X		X	X	X	X	X
Metabolic Assessments[i]		X					X		X		
Estimated GFR[j]	X	X	X	X	X		X	X	X		X
Hematology Profile[k]	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
CD4+ Cell Count	X	X	X	X	X		X	X	X	X	X
HBV and HCV Serologies[m]	X										
Plasma Sample Storage[n]		X	X	X	X	X	X	X	X		X
CCI											
Whole Blood Sample[p]	X										
HIV-1 Genotype/Phenotype[q]									X		X
Cystatin C Testing[u]		X									

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]							30 Day Follow-up	ESDD[d]
			4	8	12	16[t]	24	36	48		
Questionnaires: VAS, HIVTSQs, HIVTSQc, EQ-5D, SF-36, and FACIT-F[r]		X	X	X	X	X	X	X	X		X
Enrollment		X									
Study Drug Dispensation and Accountability		X	X	X	X	X	X	X	X[s]		X[s]

a Evaluations to be completed within 42 days prior to the Day 1 visit.
b Subjects will be dispensed study drug on the Day 1 visit; initiation of treatment with the study drug must take place within 24 hours after the Day 1 Visit. E/C/F/TAF FDC will be provided by the Sponsor.
c All study visits are to be scheduled relative to the Day 1 visit date. Visit windows are ± 2 days of the protocol specified date through Week 16, ± 6 days of the protocol specified date through Week 36, and all other study visits except Week 48. Week 48 visit window is ± 6 weeks of the protocol specified visit date, and this clinical visit window coincides with the Week 48 statistical analysis window for HIV-1 RNA.
d Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through Week 48 visit even if the subject discontinues study drug.
e Complete physical examination every 48 weeks (urogenital/anorectal exams will be performed at the discretion of the Investigator)
f Symptom-directed physical examination as needed.
g Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
h Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium and sodium. At visits in which metabolic assessments are to be performed, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.
i Metabolic Assessments: Fasting 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.
j Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
k CBC with differential and platelet count
l If the HIV-1 RNA value is ≥ 50 copies/mL a retest should be collected at a scheduled or unscheduled visit, 2-4 weeks after the date of the original test (except for screening and Day 1 results). HIV-1 genotype/phenotype resistance testing only conducted for subjects with confirmed virologic failure with HIV-1 RNA value ≥ 50 copies/mL. Subjects should be managed according to Figure 6-1, Management of Virologic Failure.
m Hepatitis B virus surface antigen serology (HBsAg) and Hepatitis C virus (HBVAb) serology (reflex HCV RNA is performed in subjects with positive HCVAb serology)
n Plasma sample storage for safety and virology testing
o CCI [redacted]
p Whole blood sample collected at Screening Visit for proviral genotype analysis of archived resistance
q HIV-1 genotype/phenotype resistance testing only conducted for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 50 copies/mL at the Week 48 and ESDD visit. Subjects should be managed according to Figure 6-1, Management of Virologic Failure. HIV-1 genotype/phenotype sample collection to occur if subjects HIV-1 RNA lab values meet the criteria described in this section.
r EQ-5D, SF-36, and FACIT-F will be administered at Day 1, Weeks 24 and 48. VAS will be administered on Day 1, Weeks 4, 8, 12, 16, 24, 36, 48 and ESDD. HIVTSQs will be administered on Day 1. HIVTSQc will be administered at Weeks 4, 24, 48 and ESDD.
s Drug accountability only; study drug will not be dispensed at this visit.
t At Week 16, subject will have only the following assessments completed: Review of AEs and changes in concomitant medications, blood sample collection for plasma HIV-1 RNA and plasma sample storage. Study drug dispensation and accountability will be documented.
u Estimated GFR according to CKD-EPI formula for cystatin clearance will be used for Nephrotoxicity Management per Section 7.5.4.

Appendix 3. Management of Clinical and Laboratory Adverse Events



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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

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

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

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypophosphatemia **Adult and Pediatric** **> 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric** **≥ 1 year** **Infant < 1 Year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN N/A	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L 1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L 0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L < 0.5 mg/dL < 27 µmol/L
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) **Adult**	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
LDL (Fasting) **Pediatric >2 to <18 years**	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

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

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

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

Notes:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1) Definitions

a) Definition of Childbearing Potential

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

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. 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 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Instructions for reporting pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

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

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

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

* Only among children aged < 6 years
† Only among adults, adolescents, and children aged ≥ 6 years
§ Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references {Centers for Disease Control and Prevention 1994}, {Centers for Disease Control and Prevention 1992}.