CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	125589
EudraCT Number:	2015-004025-14
Clinical Trials.gov Identifier:	NCT02603120
Indication:	HIV-1 Infection
Protocol ID:	GS-US-380-1844
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Protocol Version/Date:	Original: 21 October 2015 Amendment 1 19 February 2016 Amendment 2 19 October 2016

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	125589 2015-004025-14 NCT02603120
Study Centers Planned:	Approximately 100 centers in North America, Europe and Asia Pacific
Objectives:	The primary objective of this study is: • To evaluate the efficacy of switching from a regimen of DTG and ABC/3TC or a fixed dose combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF versus continuing DTG and ABC/3TC as the FDC ABC/DTG/3TC in virologically suppressed HIV-1 infected subjects as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 The secondary objectives of this study are: • To evaluate the safety and tolerability of the two treatment groups through Week 48 • To evaluate the bone safety of the two treatment groups as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Week 48
Study Design:	Randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of switching to a FDC of GS-9883/F/TAF tablet versus continuing DTG and ABC/3TC as the FDC ABC/DTG/3TC in HIV-1 infected subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of DTG + ABC/3TC or ABC/DTG/3TC FDC for ≥ 3 months prior to screening.

	Subjects who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to one of the following 2 treatment groups: **Treatment Group 1:** FDC of GS-9883 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) + Placebo to match FDC of abacavir 600 mg/ dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) administered orally, once daily, without regard to food (n=260) **Treatment Group 2:** FDC of abacavir 600 mg/dolutegravir 50 mg/ lamivudine 300 mg (ABC/DTG/3TC) + Placebo to match FDC of GS-9883 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) administered orally, once daily, without regard to food (n=260)
Number of Subjects Planned:	Approximately 520 subjects in total. 260 subjects in each Treatment Group 1 and Treatment Group 2
Target Population:	HIV-1 infected adult subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of DTG + ABC/3TC or ABC/DTG/3TC FDC for ≥ 3 months prior to screening.
Duration of Treatment:	Subjects will be treated for at least 48 weeks during the blinded treatment phase. After Week 48, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit. Once the last subject completes the Week 48 visit and Gilead completes the Week 48 analysis, all subjects will return to the clinic (preferable within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of GS-9883/F/TAF is demonstrated following review of unblinded data, subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC in an open-label (OL) extension phase for up to 96 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first. All subjects participating in the open-label extension phase, without regard to their blinded treatment regimen, will return for study visits at Week 12 OL and every 12 weeks thereafter for up to 96 weeks.

Subjects who complete the study through the End of Blinded Treatment Visit and do not continue on the open-label GS-9883/F/TAF FDC extension phase, will be required to return to the clinic 30 days after the End of Blinded Treatment visit for a 30-Day Follow-Up Visit.

Treatment assignments will be provided to the investigators within 30 days of the last subject completing the End of Blinded Treatment Visit.

Diagnosis and Main Eligibility Criteria:

Medically stable HIV-1 infected subjects who meet the following criteria:

- Currently receiving an antiretroviral regimen of DTG + ABC/3TC, or ABC/DTG/3TC FDC for ≥ 3 months prior to screening
- Currently on a stable regimen for ≥ 3 months preceding the Screening visit with documented plasma HIV 1 RNA < 50 copies/mL for ≥ 3 months preceding the Screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL).
  - Prior changes in antiretroviral regimen are only allowed due to tolerability issues or for regimen simplification. Unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or "blip") prior to screening are acceptable. If the lower limit of detection of the local HIV-1 RNA assay is <50 copies/mL (eg, <20 copies/mL), the plasma HIV-1 RNA level cannot exceed 50 copies/mL on two consecutive HIV-1 RNA tests.
- Estimated GFR ≥ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance
- No chronic Hepatitis B Virus (HBV) infection, as determined by either
  - Positive HBV surface antigen and negative HBV surface antibody, regardless of HBV core antibody status, at the screening visit
  - Positive HBV core antibody and negative HBV surface antibody, regardless of HBV surface antigen status, at the screening visit

Study Procedures/ Frequency:	After screening procedures, eligible subjects will be randomized 1:1 to Treatment Group 1 or Treatment Group 2 and treated for 48 weeks. Following the Day 1 visit, subjects will return for study visits at Weeks 4, 8, and 12, and then every 12 weeks through Week 48. After Week 48, all subjects will continue to take their blinded study drugs and attend study visits every 12 weeks until the End of Blinded Treatment Visit. For all eligible subjects, blood will be collected at Day 1, Weeks 4, 8, 12, and then every 12 weeks through the End of Blinded Treatment visit. Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count, and complete or symptom-directed physical examinations will be performed at the Screening, Day 1 and all subsequent study visits. In addition, blood will be collected and stored for possible evaluation of markers of inflammation and immune activation, which may include but not limited to: cystatin C, IL-6, hs-CRP, d-dimer, sCD14, and sCD163. Platelet function evaluations may also be assessed, including but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand. Urine will be collected for evaluations of renal tubular function including urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2 microglobulin. For all subjects on study drug, except subjects located in Germany, dual energy x-ray absorptiometry (DXA) scans will be performed prior to or within 24 hours of the Day 1 Visit, and then at Weeks 24, 48 and at the End of Blinded Treatment Visit or Early Study Drug Discontinuation Visit (blinded treatment phase only), if > 12 weeks since last scan. DXA scan results will be provided to study sites when available. Adverse events and concomitant medications will be assessed at each visit.
Test Product, Dose, and Mode of Administration:	FDC of GS-9883 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) administered orally, once daily without regard to food.
Reference Therapy, Dose, and Mode of Administration:	FDC of abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) administered orally, once daily without regard to food.

Criteria for Evaluation:

Safety:	Adverse events, clinical laboratory tests and DXA
Efficacy:	The primary efficacy endpoint is: • The proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as defined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm The secondary endpoints include: • The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm • The change from baseline in CD4+ cell count at Week 48
Pharmacokinetics:	An intensive pharmacokinetic (PK) substudy will be performed at the Weeks 4 or 8 visits in a subset of subjects (target n=30) at study sites able to conduct this testing. For all subjects on study drug a single anytime pre or post-dose PK blood sample will be collected at Weeks 8, 24 and 36. For all subjects on study drug a trough PK blood sample will be obtained 20-28 hours following the last dose at Weeks 4 and 12. Following an observed dose, one post-dose PK blood sample will be collected between 1 and 4 hours post-dose. For intensive PK substudy, the following PK parameters for GS-9883 may be explored as applicable: C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, $T_{1/2}$, AUC_{tau}, $AUC_{0\text{-}last}$, Vz/F, CLss/F The concentration of GS-9883 may be summarized using descriptive statistics. The pharmacokinetics of GS-9883 may be evaluated using population approaches. TAF and FTC concentrations may be analyzed and PK parameters may be summarized as applicable.
Optional Genomic Testing:	A separate, specific signature will be required to document a subject's agreement to provide additional samples for optional pharmacogenomic research. For subjects who agree to participate and provide their additional specific consent, three blood samples will be obtained for the extraction of DNA for genomic testing and for potential genotyping to identify polymorphisms of drug metabolism enzymes, including uridine 5'-diphospho-glucuronosyltransferase (UGT1A1) and additional biomarker testing such as human leukocyte antigen (HLA). These samples will be collected at Day 1.

	Subjects are not required to consent for optional pharmacogenomic research in order to participate in this study and have the right to withdraw their consent for optional pharmacogenomic research at any time and for any reason. The sample consented for optional pharmacogenomic research will be destroyed 15 years after the end of the study.
Patient Reported Outcome:	Short Form 36 Health Survey (SF-36), HIV Symptoms Distress Module, Work Productivity and Activity Impairment Questionnaire (WPAI) and Pittsburgh Sleep Quality Index (PSQI) will be administered at Day 1, Weeks 4, 12 and 48.
Statistical Methods:	The primary analysis will consist of a non-inferiority test of switching to FDC GS-9883/F/TAF versus continuing DTG and ABC/3TC as the FDC of ABC/DTG/3TC, with respect to the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm. It will be concluded that GS-9883/F/TAF is non-inferior to the ABC/3TC/DTG if the upper bound of the 2-sided 95% confidence interval (CI) of the difference between treatment groups (GS-9883/F/TAF – ABC/3TC/DTG) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL is less than 4%; ie, a margin of 4% is applied to non-inferiority assessment. The 2-sided 95% CIs will be constructed based on the exact method. The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm will also be summarized. The 95% CIs will be constructed in the same manner as described for the primary efficacy endpoint. The change from baseline in CD4+ cell count at Weeks 48 will be summarized by treatment using descriptive statistics. The differences and the associated 95% CIs will be constructed using an Analysis of Variance (ANOVA) model, including treatment (GS-9883/F/TAF vs. ABC/DTG/3TC) as a fixed effect in the model. The percentage change from baseline in hip and spine BMD at Week 48 will be summarized by treatment using descriptive statistics. The differences and the associated 95% CIs will be conducted using an ANOVA model, including treatment group as a fixed effect in the model. Adverse events, clinical laboratory assessment, and pharmacokinetic parameters will be summarized using descriptive statistics.

A total of approximately 520 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 treatment groups (260 subjects per treatment group), achieves at least 90% power to detect a non-inferiority margin of 4% in difference in percentage of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 between the 2 treatment groups.

For sample size and power computation, it is assumed that both treatment groups have 2% of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 (based on the historical Gilead E/C/F/TAF and STB studies), that a non-inferiority margin is 4%, and that the significance level of the test is at a one-sided 0.025 level.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
ABC/3TC	abacavir/lamivudine, Epzicom® Kivexa®
ABC/DTG/3TC	abacavir/dolutegravir/lamivudine, Triumeq®
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
BID	twice a day
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COBI, /co	cobicistat (GS-9350)
C_{tau}	the observed drug concentration at the end of the dosing interval
CPK	creatine phosphokinase
CRF	case report form(s)
CRO	contract (or clinical) research organization
CYP	cytochrome P450
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
DTG	dolutegravir, Tivicay®
ECG	electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
EVG	elvitegravir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, Stribild®
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination

FTC/TAF	emtricitabine/tenofovir alafenamide
FSH	follicle-stimulating hormone
FTC, F	emtricitabine, Emtriva®
GCP	Good Clinical Practice (Guidelines)
GGT	gamma glutamyl transferase
GLSM	geometric least squares mean
GSI	Gilead Sciences, Inc.
GS-9883/F/TAF	GS-9883/emtricitabine/tenofovir alafenamide
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDPE	high-density polyethylene
hERG	human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
HIV Sx	HIV Symptoms Distress Module
HLA	human leukocyte antigen
IB	investigator's brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug (Application)
INSTI	integrase strand-transfer inhibitors
IRB	institutional review board
IWRS	interactive web response system
KS	Kaposi's sarcoma
LDH	lactate dehydrogenase
LLN	lower limit of the normal range
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MH	Mantel-Haenszel
min	minute
mmHg	millimeters mercury
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OL	open-label
P-gp	P-glycoprotein
PI	protease inhibitor

PK	pharmacokinetic
PSQI	Pittsburgh Sleep Quality Index
PT	preferred term
PT	prothrombin time
PTM	placebo-to-match
QD	once daily
RAL	raltegravir
RNA	ribonucleic acid
SA	single agent
SAE	serious adverse eventt
SF-36	Short Form 36 Health Survey
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate, Viread®
TFV-DP	tenofovir diphosphate (TFVpp)
t_{max}	the time (observed time point) of C_{max}
TSH	thyroid stimulating hormone
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase
UGT	uridine glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus-1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest around the world. There are approximately 2.4 million people in North America and Western and Central Europe living with HIV-1 and 36 million people worldwide {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2014}. The infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function, ultimately resulting in death. Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral therapy (HAART); the introduction of HAART was associated with a dramatic decrease in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality {Palella et al 1998}, {Mocroft et al 1998}, {Sterne et al 2005}.

The success of potent and well-tolerated ART means that morbidity and mortality in the HIV-infected population is increasingly driven by non-AIDS–associated comorbidities. Clinical attention has become more focused on the optimization of tolerability, long-term safety, and adherence of potent ART regimens {Costagliola 2014}. In addition, there remains a significant medical need for new, effective therapies that take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, non-HIV comorbidities, and regimen simplification.

For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and either an integrase strand-transfer inhibitor (INSTI) or the boosted protease inhibitor darunavir {Department for Health and Human Services (DHHS) 2015}. Virologically suppressed, HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily fixed-dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Sterrantino et al 2012}, {Aldir et al 2014}

Tenofovir (TFV) is a nucleotide analog that inhibits HIV-1 reverse transcription. While tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, is a preferred NtRTI for initial therapy, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs. Tenofovir alafenamide (TAF) is also an oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF at the clinical doses. The distinct metabolism of TAF offers the potential for an improved clinical profile compared with TDF.

GS-9883 is a potent inhibitor of HIV-1 integrase that is being evaluated for the treatment of HIV-1 infection. Antiviral testing has shown that GS-9883 is active against a broad panel of HIV-1 viral lab strains and clinical isolates. GS-9883 is fully active against a panel of mutant

viruses with resistance to NRTIs, non-nucleoside reverse-transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Integrase mutant viruses that are resistant to the INSTIs raltegravir (RAL) and elvitegravir (EVG) remain largely sensitive to GS-9883.

Gilead Sciences (Gilead) has coformulated GS-9883 with the NRTI emtricitabine (FTC; F) and the NtRTI tenofovir alafenamide (TAF) into an FDC tablet that is suitable for once-daily use. This GS-9883/F/TAF FDC may provide a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients with HIV infection.

1.2. GS-9883

1.2.1. General Information

GS-9883, a potent inhibitor of HIV-1 integrase is being evaluated for the treatment of HIV infection. Antiviral testing has shown that GS-9883 is active against a broad panel of HIV-1 viral lab strains and clinical isolates. GS-9883 is fully active against a panel of mutant viruses with resistance to NRTIs, NNRTIs, and PIs. Integrase mutant viruses that are resistant to the INSTIs RAL and EVG remain largely sensitive to GS-9883.

1.2.2. Preclinical Pharmacology and Toxicology

A core battery of safety pharmacology studies have been conducted with GS-9883. These include assessments of cytotoxicity, off-target receptor and ion-channel binding, effects on human Ether-à-go-go-Related Gene (hERG) potassium current and papillary muscle action potential, and in vivo studies in rats and dogs that evaluated effects of GS-9883 on all major organ systems. The volume of distribution of GS-9883 ranged between 0.09 and 0.22 L/kg in the preclinical species, which indicates that the distribution of GS-9883 is limited to the extracellular compartment due to its high binding to plasma proteins. The projected half-life of GS-9883 in humans is approximately 20 hours based upon the estimates of clearance and volume of distribution.

1.2.2.1. Pharmacology

GS-9883 has IC_{50} values ranging from 1.5 to 2.4 nM, similar to the inhibitory effect of DTG and EVG. GS-9883 is highly potent against HIV replication in MT4 cells with an EC_{50} (50% effective inhibitory concentration) value of 1.9 nM and a protein adjusted EC_{95} value of 361 nM. GS-9883 does not show significant cytotoxicity against dividing and non-dividing human PBMCs, primary human hepatocytes and various non-target human cell lines.

GS-9883 is mainly metabolized by uridine 5'-diphospho-glucuronosyltransferase (UGT1A1) and CYP3A. GS-9883 does not inhibit major human CYP isoforms or UGT1A1 at concentrations up to 25 μM. Consequently, GS-9883 is unlikely to be a clinically relevant inhibitor of these enzymes, and is not expected to inhibit the metabolic clearance of drugs metabolized by these enzymes. GS-9883 only modestly inhibits renal transporter OCT2 (IC_{50} = 0.42 μM). As a result, GS-9883 is not expected to significantly interfere with the key transporter responsible for creatinine tubular elimination at the clinically projected $C_{max.}$ Additionally, the risk that GS-9883 will affect the OCT2-mediated excretion of co-administered drugs is considered to be low.

GS-9883 does not activate AhR and only weakly activates PXR at concentrations up to 50 μM (less than 5% and 40% of activation, respectively, compared to positive control compound). Therefore, GS-9883 is not expected to act as an inducer through PXR- or AhR-mediated pathways at the doses and exposure levels projected in clinical use.

1.2.2.2. Toxicology

Single oral doses of GS-9883 up to 1000 mg/kg were well-tolerated in rats (AD-141-2286). The increase in exposure was limited (< 2-fold) between 100 and 300 mg/kg and similar exposure was observed between 300 and 1000 mg/kg suggesting saturation of absorption at 300 mg/kg (AUC_{0-24} 2205 μg·h/mL and 1931 μg·h/mL, respectively). In monkeys, single oral doses of GS-9883 up to 1000 mg/kg were well-tolerated (AD-141-2284). The increase in exposure was limited (< 2-fold) between 300 to 1000 mg/kg (AUC_{0-24} 803 μg·h/mL and 1078 μg h/mL, respectively).

In 2-week (TX-141-2029) and 26-week (TX-141-2031) oral toxicity studies in rats at doses up to 300 mg/kg/day, GS-9883 was well-tolerated with no GS-9883-related effects on clinical observations, body weight, food consumption, ophthalmic examinations, and anatomic pathology. The high dose of 300 mg/kg/day was considered the maximum feasible dose based upon saturation of absorption. The no observed effect level (NOEL) in the 26-week study was considered to be the high dose of 300 mg/kg/day. At the NOEL, GS-9883 exposures in the rat were considered to be approximately 12-/31-fold higher (males/females) than the projected steady state human exposure of GS-9883 following administration of GS-9883/F/TAF (50/200/25 mg) QD under fed conditions.

In a 39-week study in monkeys (TX-141-2032), following administration of 1000 mg/kg/day (high dose) of GS-9883 for 39 weeks, pathology data indicated minimal to marked bile duct hyperplasia and minimal or moderate hepatocyte hypertrophy in both sexes, and minimal regenerative hyperplasia and minimal or slight neutrophil infiltrate in males. The macroscopic finding of rough surface on the liver in one male administered 1000 mg/kg/day correlated with moderate hepatocyte hypertrophy and marked bile duct hyperplasia. After a 4-week recovery period, GS-9883-related microscopic liver findings included marked bile duct hyperplasia, slight hepatocyte hypertrophy, minimal regenerative hyperplasia, and slight lymphocyte infiltrate in one male and slight bile duct hyperplasia in one female administered 1000 mg/kg/day, while the other two animals in the high dose group had no hepatobiliary findings. Minimally to mildly increased ALT activities (≤ 3.5-fold versus baseline values), likely associated with liver findings, exhibited reversibility. There were no other adverse findings in the study, including clinical observations, or effects on body weight, body weight change, food consumption, ECGs, hematology, coagulation, clinical chemistry, urinalysis, and ophthalmoscopy.

No GS-9883-related effects were observed in the mid-dose group (200 mg/kg/day) which was considered the no-observed-effect-level (NOEL). The estimated margin of exposure at the NOEL was approximately 5.1-fold based on expected human exposure with the once daily dosing of the GS-9883/F/TAF (50/200/25 mg) tablet.

A standard battery of in vitro and in vivo studies was performed to assess the genotoxic potential of GS-9883. There was no evidence of mutagenic or clastogenic activity in an in vitro bacterial reverse mutation assay (Study TX-141-2026), a chromosomal aberration assay in human lymphocytes (Study TX-141-2027), or in a rat micronucleus test (Study TX-141-2029).

1.2.3. Clinical Trials of GS-9883

Clinical trials entailing the use of GS-9883 include:

- GS-US-141-1218, a Phase 1 double blind, randomized, placebo-controlled, first-in-human, single- and multiple-ascending dose study evaluating the safety, tolerability, and PK of oral GS-9883 in healthy subjects and a randomized, open-label, 2-cohort, 3-period, crossover, PK study evaluating the drug interaction potential between F/TAF FDC tablet and GS-9883 in healthy subjects (completed)

- GS-US-141-1219, a Phase 1b randomized, double-blinded, sequential cohort placebo-controlled study of the safety, PK, and antiviral activity of GS-9883 in HIV-1 infected subjects (5 mg, 25 mg, 50 mg, 100 mg) (completed)

- GS-US-141-1233, a Phase 1,Open-label, Two-Cohort, Multiple-Period, Fixed-Sequence, Crossover Study to Evaluate 1) the Relative Bioavailability of Two GS-9883/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets Versus a GS-9883 (75 mg) Tablet and a Emtricitabine/Tenofovir Alafenamide (200/25 mg) Fixed-Dose Combination Tablet Administered Simultaneously and 2) the Effect of Food on the Pharmacokinetics of GS-9883, Emtricitabine and Tenofovir Alafenamide When Administered as GS-9883/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets (completed)

- GS-US-141-1478, a Phase 1, Open-Label, Parallel Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of GS-9883 in Subjects with Normal and Impaired Hepatic Function (in life portion completed)

- GS-US-141-1479, a Phase 1, open-label, parallel-group, adaptive single-dose study to evaluate the PK of GS-9883 in subjects with normal and impaired renal function (completed)

- GS-US-141-1480, a Phase 1 partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of GS-9883 on the QT/QTc interval in healthy subjects (completed)

- GS-US-141-1481, a Phase 1 study to evaluate the pharmacokinetics, metabolism, and excretion of GS-9883 in healthy subjects (completed)

- GS-US-141-1485, a Phase 1 adaptive study to evaluate transporter, CYP-mediated and UGT1A1 drug-drug interactions between GS-9883 and probe drugs (completed)

- GS-US-141-1487, a Phase 1 randomized, Blinded, Placebo-Controlled Phase 1 Study Evaluating the Effect of GS-9883 on Renal Function as Assessed by Markers of Glomerular Filtration Rate (completed)
- GS-US-311-1790, a Phase 1Randomized, Open Label, Drug Interaction Study Evaluating the Effect of F/TAF FDC Tablet or GS-9883 on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol (completed)
- GS-US-380-1761, a Phase 1 Study to Evaluate Pharmacokinetic Drug-Drug Interaction Potential between GS-9883/Emtricitabine/Tenofovir Alafenamide Fumarate (GS-9883/F/TAF) and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablets (completed)
- GS-US-380-1991, a Phase I Single and Multiple Dose Study Evaluating the Pharmacokinetics, Safety, and Tolerability of GS-9883/Emtricitabine/Tenofovir Alafenamide Fumarate (GS-9883/FTC/TAF) in Healthy Japanese and Caucasian Subjects (ongoing)
- GS-US-380-1999, a Phase 1 Multiple Dose Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between GS-9883/Emtricitabine/Tenofovir Alafenamide Fumarate and Sofosbuvir/Velpatasvir/GS-9857 in Healthy Subjects (completed)
- GS-US-380-3908, a Phase 1, Blinded, Placebo-controlled, Two-period Crossover Drug Interaction Study to Assess the Effect of GS-9883/F/TAF on Metformin Pharmacokinetics in Healthy Subjects (completed)
- GS-US-380-3909, a Phase 1, Open Label, Multiple-Cohort, Multiple-Period, Fixed-Sequence, Drug Interaction Study to Evaluate the Effect of Antacid and Mineral Supplements on GS-9883 Pharmacokinetics (completed)
- GS-US-141-1475, a Phase 2 Randomized, Double-Blinded Study of the Safety and Efficacy of GS-9883 + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults (ongoing)

Please refer to the GS-9883/F/TAF Investigators' Brochure for further information about these studies.

1.2.3.1. Phase 1 Safety and Pharmacokinetics

Study GS-US-141-1218 was a four part, first-in-human study. Parts A and B were randomized, double-blind, placebo-controlled, single and multiple ascending dose studies of GS-9883 in healthy male and female subjects. Part C was an open label, fixed sequence food effect study evaluating the effect of food on the PK of GS-9883. Part D was a randomized, open-label, 2-cohort, 3-period, crossover PK study evaluating the drug interaction potential between FTC/TAF FDC tablet and GS-9883 in healthy subjects.

There was no difference in the overall incidence or type of AEs when GS-9883 was administered in the fasted and fed states. There was no difference in the overall incidence of AEs when GS-9883 or FTC/TAF was each administered alone or in combination.

No deaths or pregnancies were reported. No Grade 3 or 4 AEs or SAEs, were reported in any cohort.

Increases in serum creatinine were observed in this study, presumably via inhibition of the renal transporter OCT2. In the MAD cohorts (fasted), serum creatinine change at Day 14 ranged from 0.05 mg/dL for the 5 mg cohort to 0.18 mg/dL for the 300 mg/dL cohort. In Part D (DDI), conducted in the fed state (regular meal), subjects received 100 mg GS-9883 monotherapy for 7 days and 100 mg GS-9883 with FTC/TAF for 7 days, the mean serum creatinine change at Day 7 was 0.14 mg/dL following GS-9883 and 0.17 mg/dL following GS-9883 + FTC/TAF. All changes returned to baseline after discontinuation of GS-9883.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Grade 3 laboratory abnormalities included 10 subjects with Grade 3 urine dipstick tests for blood. All of these subjects were female, none of the labs were considered by the Investigator to be clinically significant, and all were associated with menstruation. No other Grade 3 or 4 laboratory abnormalities were observed.

Based on results in study GS-US-141-1218, pharmacokinetic profile of GS-9883 was characterized by rapid absorption with time to peak plasma concentrations (median T_{max} of cohorts) ranging between 1 and 4 hours following administration under fasted conditions. GS-9883 exposures were appropriately dose proportional following single dose 25-100 mg dose administration, with decreasing dose proportional at higher doses. The half-life of GS-9883 was approximately 18 hours, with no changes observed across studied dose range as evidenced by parallel terminal phase slopes. A high-fat meal increased AUC_{inf} and C_{max} (geometric mean, 84% and 101%, respectively) following 100 mg single dose administration. Steady state was achieved after 4-6 days of once daily dosing of GS-9883 with average accumulation ratios for AUC_{24hr} of 1.6.

Table 1-1. GS-US-141-1218: GS-9883 Mean (%CV) PK Parameters Following Single Doses of GS-9883 in Healthy Subjects (GS-9883 PK Analysis Set; Part A: Single Dosing)

GS-9883 PK Parameter Mean (%CV)	5mg (N=6)	25 mg (N=6)	50 mg (N=6)	100 mg (N=6)	300 mg (N=6)	600 mg (N=6)
C_{max} (ng/mL)	691.2 (22.1)	1618.3 (26.7)	3965.0 (40.1)	6998.3 (36.1)	14605.0 (27.1)	20050.0 (7.5)
T_{max} (hr)	1.25 (1.00-1.50)	2.00 (1.00-3.00)	3.00 (1.50-4.00)	2.25 (1.50-3.00)	3.50 (2.00-6.00)	3.5 (2.00-4.00)
AUC_{inf} (ng.hr/mL)	13059.7 (25.1)	35718.2 (21.3)	78399.5 (29.7)	163028.2 (24.3)	355917.3 (32.9)	454446.8 (19.9)
$T_{1/2}$ (hr)	18.51 (16.81-19.99)	18.08 (16.63-19.64)	16.72 (15.77-17.11)	18.90 (17.96-20.05)	18.14 (17.86-20.53)	17.89 (16.38-19.52)

$T_{1/2}$ and T_{max}: Median (Q1, Q3)

Table 1-2 presents GS-9883 plasma PK parameters following administration of GS-9883 (5, 25, 50, 100, and 300 mg) once daily for 7 days. Following administration of either GS-9883 (5, 25, 50, 100, or 300 mg) once daily for 7 days, the PK absorption profile observed on Days 1 and 7 was similar to that observed in Part A (SAD). The median T_{max} values ranged from 1.5 to 2.5 hours on Day 1 and 1.5 to 4.0 hours on Day 7. Linearity was observed comparing GS-9883 AUC and C_{max} on Days 1 and 7 over the dose range of 25 to 50 mg. Steady state levels of GS-9883 were achieved between Study Days 4 to 6 of dosing and maintained through Day 14. Accumulation is approximately 1.6-fold, which is consistent with the observed half-life of the GS-9883 (approximately 18 hours).

Table 1-2. GS-US-141-1218: GS-9883 Plasma Pharmacokinetic Parameters by GS-9883 Dose Following Multiple-Dose Administration of GS-9883 (Analysis Set: GS-9883 PK Part B: Multiple-Dose)

	GS-9883 PK Parameter Mean (%CV)[a]	Multiple-Dose GS-9883				
		5 mg (N = 6)	25 mg (N = 6)	50 mg (N = 6)	100 mg (N = 6)	300 mg (N = 6)
Day 1	AUC_{0-24} (hr*ng/mL)	9033.6 (8.2)	27,775.1 (28.3)	58,371.4 (18.9)	79,773.8 (18.9)	180,714.3 (17.6)
	C_{max} (ng/mL)	709.7 (9.5)	2220.0 (35.6)	4648.3 (18.7)	6248.3 (26.8)	13,716.7 (19.1)
	T_{max} (hr)	1.50 (1.50, 1.50)	1.75 (1.00, 3.00)	1.50 (1.00, 2.00)	2.50 (2.00, 3.00)	2.50 (2.00, 4.00)
Day 7	AUC_{tau} (hr*ng/mL)	14,392.0 (16.7)	50,008.2 (26.6)	89,710.1 (22.7)	126,785.8 (23.7)	277,200.2 (16.7)
	C_{max} (ng/mL)	982.5 (7.9)	3455.0 (24.1)	6538.3 (17.6)	9396.7 (20.8)	19,900.0 (21.2)
	C_{tau} (ng/mL)	400.83 (26.9)	1322.00 (27.8)	2241.67 (28.2)	3145.00 (26.1)	6758.33 (21.6)
	T_{max} (hr)	1.50 (1.00, 2.00)	3.00 (2.00, 3.00)	1.75 (1.50, 2.00)	1.75 (1.50, 3.00)	4.00 (2.00, 4.00)
	Accumulation Ratio of AUC (%)	160.5 (19.0)	182.2 (17.1)	154.0 (15.9)	158.5 (12.1)	157.5 (22.6)

a Data are presented as mean (%CV), except for T_{max}, and $t_{½}$, which are presented as median (Q1, Q3)

Table 1-3 presents the GLSM ratios and associated 90% CIs for the test (fed) versus reference (fasted) treatments for the primary plasma PK parameters of GS-9883. Administration of a single dose of GS-9883 100 mg with food (high-calorie/high-fat breakfast) increased the GLSM values of C_{max} and AUC_{inf} 101% (90% CI of GLSM ratio 165.93% to 242.74%) and 84% (90% CI of GLSM ratio 152.05% to 222.59%), respectively. There were no apparent changes in clearance and $T_{1/2}$ following administration with food, indicating that food enhanced the bioavailability of GS-9883 by improving its solubility and/or absorption.

Table 1-3. GS-US-141-1218: Statistical Comparison of GS-9883 Pharmacokinetic Parameters Following Single-Dose Administration of GS-9883 in the Fasted and Fed States (GS-9883 PK Analysis Set)

GS-9883 PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Test GS-9883 100 mg Fed (n=8)	Reference GS-9883 100 mg Fasted (n=8)	
AUC_{inf} (hr*ng/mL)	214,146.3 (15.9)	117,777.1 (23.3)	183.97 (152.05, 222.59)
AUC_{last} (hr*ng/mL)	209,259.9 (15.1)	115,681.7 (24.0)	183.58 (151.91, 221.86)
C_{max} (ng/mL)	11,268.8 (15.1)	5885.0 (34.9)	200.69 (165.93, 242.74)

CI = confidence interval; GLSM = geometric least squares mean

1.2.3.2. Phase 1b Proof of Concept

The first HIV-1 positive human subjects were dosed in the fasted state with 10 days of GS-9883 in study (GS-US-141-1219). Four cohorts of 5 subjects each were randomized 4:1 to receive GS-9883 or placebo to match at doses of 5 mg, 25 mg, 50 mg, and 100 mg once daily for 10 days.

GS-9883 was generally well tolerated at the doses evaluated. A total of 9 of 20 subjects had an AE in this study. The most frequently reported AEs across all subjects were diarrhea (2 subjects), and headache (3 subjects). No other AE was reported in more than 1 subject. There was no increase in the incidence of AEs with increasing doses of GS-9883.

The majority of AEs were considered by the investigator to be not related to study drug. A total of 2 subjects experienced mild diarrhea that was considered related to study drug (1 in the 5 mg cohort, 1 in the 100 mg cohort).

No deaths or pregnancies were reported. No Grade 3 or 4 AEs, SAEs, or AEs leading to discontinuation of study drug were reported in any cohort.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. No Grade 3 treatment emergent laboratory abnormalities were observed. Median serum creatinine changes at Day 10 were: 0.05 mg/dL (5 mg), 0.04 mg/dL (25 mg), 0.06 mg/dL (50 mg), and 0.15 mg/dL (100 mg). These changes in serum creatinine appeared to be transient and returned close to baseline values on discontinuation of study drug. One Grade 4 new onset laboratory abnormality was seen in 1 subject who received 5 mg GS-9883. This was a Grade 4 CPK seen on Day 17, 7 days following his last dose of study medication. The subject was asymptomatic. The Investigator felt that this was unrelated to study medication and was due to resumption of crystal methamphetamine use by the subject. An adverse event of elevated CK was reported unrelated to study medication.

Based on PK information collected in study GS-US-141-1219, which was in line with PK observed in study GS-US-141-1218, the median IQ for each dose were calculated and are presented in Table 1-4 below.

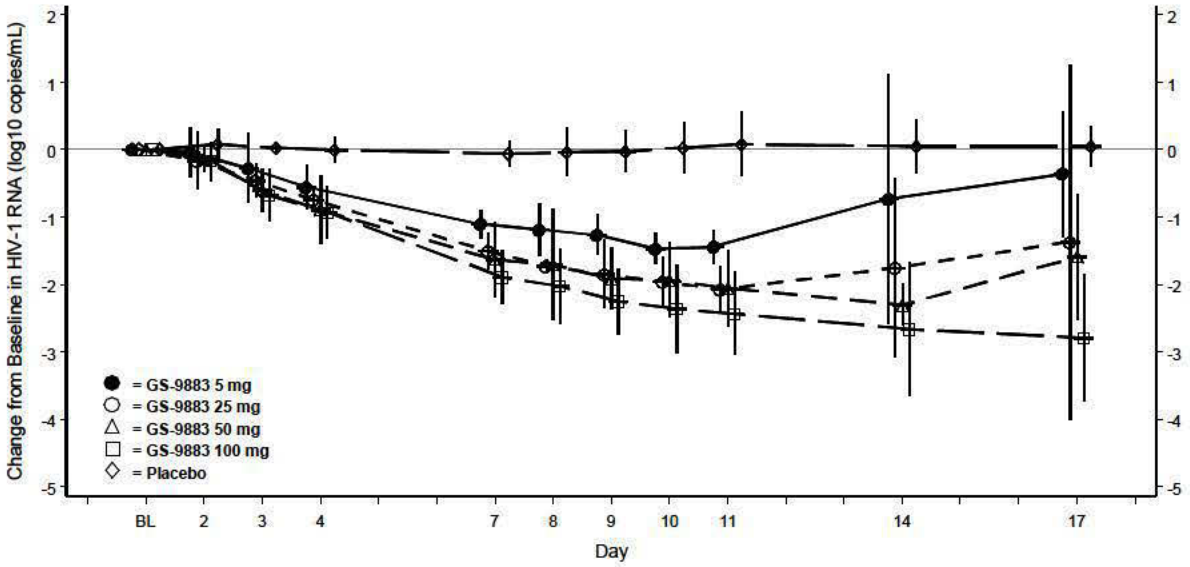
Table 1-4. Trough GS-9883 Plasma Concentrations at Steady State Following GS-9883 Administration Under Fasting Conditions and Corresponding Protein-Adjusted IQ_{95} Values (GS-9883 PK Analysis Set)

GS-9883 dose	n	Median (range) $C_{tau,SS}$ (ng/mL)	Median (range) $paIQ_{95}$[a]
5 mg	4	206.5 (146.0 to 342.0)	1.3 (0.9 to 2.1)
25 mg	4	797.5 (714.0 to 1900.0)	4.9 (4.4 to 11.7)
50 mg	4	2170.0 (852.0 to 3020.0)	13.4 (5.3 to 18.6)
100 mg	4	4190.0 (3730.0 to 5970.0)	25.9 (23.0 to 36.9)

a. The protein adjusted IQ95 (paIQ95) value is estimated based on steady-state Ctau values and the in vitro paIC95 value for wild-type HIV-1 (162 ng/ml).

The mean and 95% CIs of change from baseline in HIV-1 RNA (log_{10} copies/mL) are presented in Figure 1-1.

Figure 1-1. GS-US-141-1219: Mean and 95% CIs of Change from Baseline in HIV-1 RNA (log_{10} copies/mL) (PP Analysis Set)



GS-9883 5 mg (n=):	3	3	3	3	3	3	3	3	3	3	3
GS-9883 25 mg (n=):	4	3	4	3	4	4	4	4	4	4	3
GS-9883 50 mg (n=):	4	4	4	4	4	4	4	4	4	4	4
GS-9883 100 mg (n=):	4	4	4	3	4	4	4	4	4	4	4
Placebo (n=):	4	4	4	4	4	4	4	4	4	4	4

NOTE: Baseline value was the last available value collected prior to the time of the first dose of study drug.

Mean viral load change on Day 11 was -2.08 log_{10} in the 25 mg cohort, -2.06 log_{10} in the 50 mg cohort, and -2.43 log_{10} in the 100 mg cohort. Time weighted average change from baseline at Day 11 (DAVG11) was -0.92 log_{10} in the 5 mg cohort, -1.33 log_{10} in the 25 mg

cohort, -1.37 log_{10} in the 50 mg cohort and -1.61 log_{10} in the 100 mg cohort. Viral suppression (HIV-1 RNA < 50 copies/mL) was ever achieved by the end of the study (Day 17) by 1 subject (25.0%) in the GS-9883 50 mg group and 2 subjects (50%) in the GS-9883 100 mg group.

1.2.3.3. Summary of Phase 2 Study (GS-US-141-1475)

Study GS-US-141-1475 is an ongoing Phase 2, randomized, double-blind, multicenter, active-controlled study to assess the safety and efficacy of a regimen containing GS-9883+F/TAF versus dolutegravir (DTG)+F/TAF in HIV-infected, ART-naive adult subjects.

Eligible subjects were randomized in a 2:1 ratio to one of the following treatment groups, stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL, or > 400,000 copies/mL) at screening:

- Treatment Group 1: GS-9883 75 mg + F/TAF (200/25 mg) + placebo-to-match DTG 50 mg once daily
- Treatment Group 2: DTG 50 mg + F/TAF (200/25 mg) + placebo-to-match GS-9883 75 mg once daily

Week 24 interim data are summarized below.

Subject Disposition and Baseline Characteristics

A total of 98 subjects were randomized and treated in the study: 65 subjects in the GS-9883+F/TAF group and 33 subjects in the DTG+F/TAF group. At the time of the Week 24 data analysis, 2 subjects (2.0%) had prematurely discontinued from the study, 1 in each treatment group; both subjects were lost to follow-up.

Demographic and baseline characteristics were similar between the 2 treatment groups.

Key baseline disease characteristics (ie, viral load, CD4 cell count, and $eGFR_{CG}$) were similar between the 2 treatment groups.

Median (first quartile [Q1], third quartile [Q3]) baseline HIV-1 RNA was 4.45 (3.96, 4.79) log_{10} copies/mL, with 82.7% of subjects having ≤ 100,000 copies/mL at baseline; 5 subjects had > 400,000 copies/mL at baseline; 4 of these subjects were randomized to GS-9883+F/TAF and 1 subject was randomized to DTG+F/TAF.

Median (Q1, Q3) baseline CD4 cell count was 444 (316, 595) cells/µL, with 41.8% of subjects having ≥ 500 cells/µL at baseline. Median (Q1, Q3) baseline $eGFR_{CG}$ was 125.3 (105.7, 147.0) mL/min.

Efficacy Results

Virologic success at Weeks 12 and 24 was assessed using the US FDA-defined snapshot algorithm, defined as plasma HIV-1 RNA < 50 copies/mL. At Weeks 12 and 24, virologic success was high and similar between the 2 treatment groups as follows: Week 12 GS-9883+F/TAF 93.8%, DTG+F/TAF 93.9% (stratum-adjusted difference in percentages: −1.3%; 95% CI: −12.9% to 10.2%; p = 0.79); Week 24 GS-9883+F/TAF 95.4%, DTG+F/TAF 93.9% (1.0%; 95% CI: −10.7% to 12.7%; p = 0.84).

Of the 5 subjects with baseline viral load > 400,000 copies/mL, 4 had HIV-1 RNA < 50 copies/mL at Week 24, and had 60 copies/mL.

Following initiation of study drug, the increases from baseline in CD4 cell count were similar between treatment groups. Mean (SD) baseline CD4 cell counts were as follows: GS-9883+F/TAF 471 (190.9) cells/µL; DTG+F/TAF 507 (271.0) cells/µL; p = 0.35. The mean (SD) change in CD4 cell count from baseline to Week 12 was similar between the 2 treatment groups as follows: GS-9883+F/TAF, +170 (150.0) cells/µL; DTG+F/TAF, +173 (220.5) cells/µL (difference in least squares mean [LSM]: 0; 95% CI: −76 to 76; p = 1.00). There were similar increases in the mean (SD) CD4 cell count in both treatment groups Week 24: GS-9883+F/TAF, +189 (177.8) cells/µL; DTG+F/TAF, +157 (163.2) cells/µL (difference in LSM: 39; 95% CI: −35 to 113; p = 0.30).

Interim Virology Resistance Data

Through Week 24, no emergent drug resistance was detected.

Safety Results

Adverse Events

The overall incidence of treatment-emergent AEs was balanced between treatment groups as follows: GS-9883+F/TAF 66.2%, 43 subjects; DTG+F/TAF 57.6%, 19 subjects. The most common treatment-emergent AEs (occurring in > 2 subjects) by treatment group were as follows:

- **GS-9883+F/TAF:** diarrhea and headache (7.7%, 5 subjects each); and nausea, decreased appetite, arthralgia, and cough (4.6%, 3 subjects each)
- **DTG+F/TAF:** nausea (12.1%, 4 subjects); diarrhea (9.1%, 3 subjects)

Most treatment-emergent AEs were Grade 1 in severity. Grade 3 or 4 AEs were reported in only 1 subject (Grade 3 diabetic ketoacidosis), in the GS-9883+F/TAF group; this event was also reported as an SAE. One other SAE (appendicitis), also in the GS-9883+F/TAF group, was reported. Neither SAE was considered related to study drug by the investigator or resulted in study drug discontinuation or interruption, and both SAEs resolved.

The overall incidence of study drug-related treatment-emergent AEs was balanced between treatment groups as follows: GS-9883+F/TAF 15.4%, 10 subjects; DTG+F/TAF 18.2%, 6 subjects. Most study drug-related treatment-emergent AEs were Grade 1 in severity. Grade 2

study drug-related treatment-emergent AEs were reported in 1 subject in the GS-9883+F/TAF group (somnolence and headache) and 1 subject in the DTG+F/TAF group (vomiting). There were no Grade 3 or 4 treatment-emergent AEs or SAEs reported that were considered related to study drug.

No Grade 4 AEs, deaths, pregnancies, or AEs leading to premature study drug discontinuation were reported in either treatment group.

Clinical Laboratory Evaluations

The percentage of subjects with at least 1 treatment-emergent laboratory abnormality (ie, at least 1 grade level increase from baseline in graded abnormality) was similar between treatment groups as follows: GS-9883+F/TAF 76.6%, 49 subjects; DTG+F/TAF 78.1%, 25 subjects. The majority of treatment-emergent laboratory abnormalities were Grade 1 or 2 in severity. The percentage of subjects with at least 1 Grade 3 or 4 treatment-emergent laboratory abnormality was similar between treatment groups as follows: GS-9883+F/TAF 17.2%, 11 subjects; DTG+F/TAF 12.5%, 4 subjects. Grade 3 or 4 laboratory abnormalities occurring in at least 2 subjects in either treatment group were as follows: creatine kinase (GS-9883+F/TAF, 7.8% [5 subjects]), fasting serum glucose (DTG+F/TAF, 6.3% [2 subjects]), aspartate aminotransferase (AST) (GS-9883+F/TAF, 3.1% [2 subjects]), and fasting low-density lipoprotein (LDL) (GS-9883+F/TAF, 3.1% [2 subjects]). The only Grade 4 laboratory abnormalities were for creatine kinase, reported in 2 subjects (3.1%) in the GS-9883+F/TAF group. All increased creatine kinase values appeared to be transient, and none were associated with AEs. Of the 2 subjects with increased AST, 1 subject had Grade 3 AST and Grade 3 ALT at Week 24 in the setting of alcohol abuse; the other subject had Grade 3 AST at Week 8 that returned to normal by Week 24.

There were no clinically significant changes from baseline or differences between treatment groups in the median values for hematology, chemistry, or metabolic parameters. There were similar increases from baseline in median (Q1, Q3) serum creatinine in both treatment groups at Week 24: GS-9883+F/TAF 0.12 (0.06, 0.18) mg/dL; DTG+F/TAF 0.13 (0.05, 0.21) mg/dL. There were decreases in median (Q1, Q3) $eGFR_{CG}$ at Week 24, which were smaller in the GS-9883+F/TAF compared with the DTG+F/TAF group: GS-9883+F/TAF −13.3 (−19.9, −4.0) mL/min; DTG+F/TAF −17.2 (−25.7, −6.9) mL/min.

Conclusions

Key Week 24 conclusions from Study GS-US-141-1475 include the following:

- Virologic success at Week 24 when assessed using the US FDA-defined snapshot algorithm, defined as plasma HIV-1 RNA < 50 copies/mL, was similar between the 2 treatment groups as follows: GS-9883+F/TAF 95.4%; DTG+F/TAF 93.9%; stratum-adjusted difference in percentages: 1.0%; 95% CI: −10.7% to 12.7%; p = 0.84. There was a similar increase in the mean (SD) CD4 cell count between the 2 treatment groups, GS-9883+F/TAF, +189 (177.8) cells/µL; DTG+F/TAF, +157 (163.2) cells/µL (difference in LSM: 39; 95% CI: −35 to 113; p = 0.30).

- No resistance to any INSTIs, NRTIs, NNRTIs, or PIs was detected through Week 24.
- No AEs led to study drug discontinuation in either treatment group.

Both GS-9883+F/TAF and DTG+F/TAF were generally well tolerated through 24 weeks of treatment. The most commonly reported treatment-emergent AEs were diarrhea and headache (7.7% each) in the GS-9883+F/TAF group and nausea (12.1%) and diarrhea (9.1%) in the DTG+F/TAF group. There were 2 SAEs, 1 of which was also a Grade 3 AE; neither of these events was considered related to study drug by the investigator, or led to study drug discontinuation. There were no other Grade 3 or 4 AEs, and no deaths, pregnancies, or AEs leading to premature study drug discontinuation reported. The percentage of subjects with at least 1 treatment-emergent laboratory abnormality was similar between treatment groups. The majority of treatment-emergent laboratory abnormalities were Grade 1 or 2 in severity. There were similar increases from baseline in serum creatinine in both treatment groups at Week 24.

1.3. Information about Emtricitabine (Emtriva®, FTC)

Emtricitabine (5-fluoro-1-[(2R, 5S)-2-(hydroxymethyl)-[1, 3]-oxathiolan-5-yl] cytosine, FTC) is a NRTI that has demonstrated potent and selective inhibition of the HIV. In HIV-infected adults, FTC is administered as a 200 mg QD dose concurrently with other ARVdrugs. The 200 mg FTC capsule formulation was approved by the US FDA for marketing on 2 July 2003 and is available under the name Emtriva®. In the European Union (EU), marketing authorization was granted for both the 200 mg Emtriva® capsule formulation and a 10 mg/mL Emtriva® oral Solution formulation on 24 October 2003, with indications for the treatment of HIV infection concurrently with other antiretroviral drugs in both adult and pediatric patients.

Further information is available in the current Prescribing Information for Emtriva®.

1.4. Information about Tenofovir alafenamide (TAF, GS-7340)

Tenofovir alafenamide (GS-7340, TAF) 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. 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.

Please refer to the GS-9883/F/TAF Investigator's Brochure for further information.

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

Clinical trials entailing the use of tenofovir alafenamide include:

- GS-US-120-1101, a Phase 1/2 study of the pharmacokinetics and antiviral activity of GS-7340 (50 mg and 150 mg) in HIV-infected subjects (completed)

- GS-US-120-0104, a Phase 1b study of the pharmacokinetics and antiviral activity of GS-7340 (8 mg, 25 mg, 40 mg) in HIV infected subjects (completed)
- GS-US-120-0107, a Phase 1, partially-blinded, randomized, placebo- and positive controlled study to evaluate the effect of GS-7340 on the QT/QTc interval in healthy subjects (completed)
- GS-US-120-0108, a Phase 1, open-label, parallel-design study to evaluate the pharmacokinetics of GS-7340 in subjects with severe renal impairment (completed)
- GS-US-120-0109, a Phase 1 study to evaluate the pharmacokinetics, metabolism and excretion of GS-7340 (completed)
- GS-US-120-0114, a Phase 1, open-label, parallel-group, single dose study to evaluate the pharmacokinetics of tenofovir alafenamide in subjects with normal and impaired hepatic function (completed)
- GS-US-120-0117, a Phase 1 single-dose study evaluating the pharmacokinetic drug interaction potential between rilpivirine and tenofovir alafenamide (completed)
- GS-US-120-0118, a Pharmacokinetic study evaluating the drug interaction potential of tenofovir alafenamide with a boosted protease inhibitor or unboosted integrase inhibitor in healthy subjects (completed)
- GS-US-120-1538, a Fixed-Sequence, Open-Label, Study Evaluating the Pharmacokinetics and Drug Interaction Potential between Tenofovir Alafenamide and Midazolam (Oral and Intravenous) in Healthy Volunteers (completed)
- GS-US-120-1554, a Fixed-Sequence, Randomized, Open-Label, 2-Cohort, 2-Period, Multiple-Dose Study Evaluating the Pharmacokinetics and Drug Interaction Potential between Tenofovir Alafenamide and Rilpivirine in Healthy Subjects (completed)
- GS-US-311-1386, a Phase 1 study to determine the effect of food on the pharmacokinetics of tenofovir alafenamide when administered as F/TAF FDC in healthy volunteers (completed)
- GS-US-311-0101, a Phase 1 healthy volunteer study evaluating the drug interaction potential between once-daily FTC/GS-7340 fixed-dose combination and efavirenz (EFV) or COBI-boosted darunavir (DRV) (completed)
- GS-US-311-1088, a Phase 1, Relative Bioavailability Study of Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet to evaluate the formulation performance of emtricitabine (FTC) and tenofovir alafenamide (TAF) fixed dose combination tablets relative to co-administration of individual agents (completed)
- GS-US-311-1089, a Phase 3 study of the safety and efficacy of FTC/TAF in HIV infected, virologically suppressed patients (ongoing)

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

1.4.2. Clinical Trials of FTC/TAF as part of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF)

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

- GS-US-292-0101, a Phase 1 healthy volunteer study evaluating the relative bioavailability of EVG, FTC, TFV, and COBI administered as E/C/F/TAF STR relative to E/C/F/TDF or TAF (completed)
- GS-US-292-0103, a Phase 1 healthy volunteer study to evaluate the pharmacokinetics and relative bioavailability of the E/C/F/TAF STR relative to the individual components at GS-7340 doses of 10 mg (STR) or 25 mg Single Agent (SA) (completed)
- GS-US-292-0102, a Phase 2 randomized, double-blinded study of the safety and efficacy of E/C/F/TAF STR versus E/C/F/TDF STR in HIV-1 infected, antiretroviral treatment-naive adults (ongoing)
- GS-US-292-0104 and GS-US-292-0111, Phase 3 randomized, double-blinded study of the safety and efficacy of E/C/F/TAF STR versus E/C/F/TDF STR in HIV-1 infected, antiretroviral treatment-naive adults (ongoing)
- GS-US-292-0109, a Phase 3 open-label study to evaluate switching from a TDF-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed, HIV-1 positive subjects (ongoing)
- GS-US-292-0112, a Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide single-tablet Regimen in HIV-1 positive patients with mild to moderate renal impairment (ongoing)
- GS-US-292-0117, a Phase 3, two-part study to evaluate the efficacy of Tenofovir Alafenamide versus placebo added to a failing regimen followed by treatment with Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1 positive, antiretroviral treatment-experienced adults (ongoing)

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

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

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

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

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

Studies GS-US-292-0104 and GS-US-292-0111 are ongoing, Phase 3 randomized, double-blinded studies of the safety and efficacy of E/C/F/TAF versus E/C/F/TDF in HIV-1 infected, antiretroviral treatment-naive adults. The interim Week 48 key conclusions from pooled data showed that E/C/F/TAF once daily was noninferior to STB once daily when administered for 48 weeks to HIV-infected, ART-naive adults, as assessed using the US FDA-defined snapshot algorithm with HIV-1 RNA < 50 copies/mL (E/C/F/TAF 92.4%; STB 90.4%; difference in percentages: 2.0%, 95% CI: -0.7% to 4.7%). Administration of E/C/F/TAF resulted

in > 90% lower plasma TFV and higher intracellular TFV-DP relative to STB. E/C/F/TAF showed an improved renal and bone safety profile with significantly less decline in hip and spine BMD, less increase in serum creatinine and reduction in estimated glomerular filtration rate (eGFR).

1.5. Information about GS-9883/emtricitabine/tenofovir alafenamide (GS-9883/F/TAF)

Please refer to the GS-9883/F/TAF Investigator's Brochure for further information.

1.5.1. GS-US-141-1233: Relative Bioavailability of GS-9883, FTC, and TAF between GS-9883/F/TAF and GS-9883 + F/TAF

Study GS-US-141-1233 is an ongoing Phase 1, open-label, 2-cohort, multiple-period, fixed-sequence, crossover study conducted at a single center in the US to evaluate 1) the relative bioavailability (BA) of 2 GS-9883/F/TAF (75/200/25 mg and 50/200/25 mg) FDC tablets compared with the GS-9883 (75 mg) tablet and the F/TAF (200/25 mg) FDC tablet administered simultaneously and 2) the effect of food on the PK of GS-9883, FTC, and TAF when administered as GS-9883/F/TAF (75/200/25 mg and 50/200/25 mg) FDC tablets.

Cohort 1 evaluated the relative BA and food effect of GS-9883/F/TAF (75/200/25 mg) FDC tablet in a 3-period sequence. Following review of preliminary data from Cohort 1, Cohort 2 was added to the study via protocol amendment. Cohort 2 evaluated the relative BA and food effect of GS-9883/F/TAF (50/200/25 mg) FDC tablet in a 4-period sequence.

The in-life portion of Cohorts 1 and 2 are complete. Preliminary results are summarized below.

Cohort 1 Results:

- Pharmacokinetic Results

- Under fasted conditions, GS-9883 AUC_{inf} and C_{max} were 27% and 31% higher, respectively, following GS-9883/F/TAF (75/200/25 mg) FDC administration than following administration of single-agent GS-9883 (75 mg) with the F/TAF (200/25 mg) FDC. FTC and TAF exposure was similar following administration of GS-9883/F/TAF (75/200/25 mg) or single-agent GS-9883 (75 mg) with the F/TAF (200/25 mg) FDC. Compared with administration under fasted conditions, administration of the GS-9883/F/TAF (75/200/25 mg) FDC with a high-fat meal resulted in a 46% higher GS-9883 AUC_{inf} and a 27% higher GS-9883 C_{max}. The impact of food on TAF and FTC exposure was similar to that previously observed for F/TAF (Study GS-US-311-1386). GS-9883/F/TAF may be taken without regard to food. Based on these results, Cohort 2 was added to the study via protocol amendment to evaluate the relative BA of the GS-9883/F/TAF (50/200/25 mg) FDC tablet compared with the single-agent GS-9883 (75 mg) tablet and the F/TAF (200/25 mg) FDC tablet administered simultaneously.

Safety Results

Of the 28 subjects included in the Safety Analysis Set for Cohort 1, 12 subjects (43%) had at least 1 treatment-emergent AE. All treatment emergent AEs were assessed as Grade 1 or 2 in severity. No deaths or other SAEs occurred during this study, and no subject discontinued the study due to an AE.

Cohort 2 Results:

Pharmacokinetic Results

The PK results from Study GS-US-141-1233 demonstrated that the GS-9883 AUC_{inf} and C_{max} following administration of the 50mg GS-9883 FDC tablets was 79% and 78%, respectively of those observed in the same study following co-administration of GS-9883 75 mg single agent with F/TAF (200/25 mg) under fasted conditions. The GS-9883 exposures of 50 and 75 mg fixed dose combination tablets were approximately dose proportional under fasted and fed conditions and a high fat and moderate fat meal had similar impact on GS-9883 with AUC_{inf} increasing by 24%. The steady state ${}_{pa}IQ_{95}$ of GS-9883/F/TAF (50/200/25 mg) was predicted to be 17 (fasted)-23 (fed). The exposures of TAF and FTC of the 50 mg GS-9883 FDC were similar to those of GS-9883 75 mg single agent with F/TAF FDC, and the food effect on TAF and FTC was similar to the historical results.

Safety Results

Of the 28 subjects included in the Safety Analysis Set for Cohort 2, 12 subjects (43%) had at least 1 treatment-emergent AE. All treatment emergent AEs were assessed as Grade 1 or 2 in severity. No deaths or other SAEs occurred during this study, and no subject discontinued the study due to an AE.

1.6. Information about abacavir/dolutegravir/lamivudine (ABC/DTG/3TC Triumeq®)

For more detailed information, refer to the current Prescribing Information and local product labeling for abacavir/dolutegravir/lamivudine.

1.7. Rationale for this Study

HIV standard of care has relied upon nucleos(t)ide backbones for effective and durable virologic suppression, but nucleos(t)ide-associated toxicities are increasingly important as HIV-infected patients are often diagnosed earlier, initiate therapy earlier, and look toward lifelong therapy (often greater than 50 years). Where patients have access to treatment, morbidity and mortality are driven by non–AIDS-associated comorbidities, which are observed earlier than in HIV-uninfected age-matched controls despite the best available ART. The contribution of specific nucleos(t)ides, including abacavir and tenofovir disoproxil fumarate, to long-term morbidity and mortality is increasingly important in this context.

The GS-9883/F/TAF FDC has the potential to offer a simple, once-daily regimen containing a second generation INSTI that provides a high barrier to resistance, does not require a boosting agent, and offers an effective and safer alternative to standard nucleos(t)ide based regimens, without the need for HLA testing or close monitoring of renal or bone toxicities. It could provide a FDC treatment that avoids the risk of hypersensitivity reactions, would not contribute to an increased risk of cardiovascular events; could be used in patients with chronic hepatitis B or C infection or renal impairment, and that could be continued as patients age and confront non-HIV-related comorbidities.

The objective of this study is to evaluate the efficacy of switching from a regimen of DTG and ABC/3TC or a Fixed dose combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF versus continuing DTG and ABC/3TC as the FDC ABC/DTG/3TC in virologically suppressed HIV-1 infected subjects as determined by the proportion of subjects with virologic failure (HIV-1 RNA ≥ 50 copies/mL) at Week 48. ABC/DTG/3TC was selected as the active comparator for this study as it is a second-generation integrase inhibitor-based, once-daily fixed dose combination, and is a DHHS Guidelines preferred regimen that includes the 3TC/ABC backbone. Use of ABC/DTG/3TC as a comparator in this study will therefore allow comparison of two single tablet regiments containing second generation, unboosted INSTIs.

1.8. Risk/Benefit Assessment for the Study

All patients with HIV-1 infection should receive effective antiretroviral therapy. Potential risks associated with all classes of ARVs include immune reconstitution syndrome, lipodystrophy, and lactic acidosis with steatosis. The risk of class effects is considered to be low. Important identified risks appropriately managed by study inclusion/exclusion criteria as well as through close clinical and laboratory monitoring during the study, are as follows: hypersensitivity reaction to abacavir and allergy to any components of the tablets. Some observational studies have shown increased risk of cardiovascular disease with abacavir. Interim data will also be reviewed by an independent data monitoring committee. Potential benefits may include provision of a new antiretroviral therapy that is not currently available and which may have fewer side effects than alternative therapies. Other potential benefits include provisions of fixed dose combination therapy, and the knowledge that patient participation will contribute to the body of knowledge of HIV therapies.

Following a chronic 39 week study in monkeys, animals administered the highest dose of GS-9883 (1000 mg/kg/day) had bile duct hyperplasia (increased cell growth) and hypertrophy (increased cell size), and some increased cell growth and inflammation in nearby liver cells. These effects were not seen in monkeys administered the mid-level dose (200 mg/kg/day), and these animals had plasma GS-9883 exposures that were approximately 5-fold above human exposures when given the GS-9883/F/TAF FDC. No adverse drug reactions associated with liver or bile duct problems has been identified in humans treated with GS-9883. Potential hepatobiliary toxicity is appropriately managed by study inclusion/exclusion criteria, close clinical and laboratory monitoring, as well as specific toxicity management guidance to investigators (Refer to Section 7.5.5).

The overall benefit-risk assessment for GS-9883/F/TAF is favorable at this time.

1.9. Rationale for Dose Selection

FTC

The 200 mg dose of FTC represents the marketed dose for this agent that is currently available as single agent capsules (EMTRIVA) and as a component of a number of fixed-dose combination tablets, including: TRUVADA, ATRIPLA, COMPLERA (EVIPLERA), and STRIBILD.

TAF

Based upon results of the Phase 1 Study GS-US-120-0104, in which various doses of TAF (8 mg, 25 mg, and 40 mg) were administered to HIV-infected subjects in 10 days of monotherapy, the range of exposure achieved with TAF 25 mg was chosen as the reference exposure. In this study, TAF 25 mg resulted in near-maximal antiviral activity and plasma TFV exposure > 90% lower relative to TDF.

The recommended dose of TAF is based on ensuring that patients have a TAF systemic exposure that is within the range of the reference exposure achieved with TAF 25 mg, or with TAF 10 mg when administered with the boosting agent COBI as E/C/F/TAF, for which an extensive safety and efficacy database exists. Specifically, TAF 25 mg is recommended with third agents that do not have a clinically relevant effect on TAF exposure. Study GS-US-141-1418 showed that GS-9883 does not have a clinically relevant effect on TAF exposure. Therefore, the dose of TAF 25 mg is appropriate for the GS-9883/F/TAF FDC.

GS-9883

The dose of GS-9883 for Phase 2 was selected based upon data from Study GS-US-141-1219 (Table 1-5), in which HIV-1-infected subjects were administered 5, 25, 50, or 100 mg doses of GS-9883 monotherapy under fasting conditions for 10 days.

Table 1-5. GS-US-141-1219: Trough GS-9883 Plasma Concentrations at Steady State Following GS-9883 Administration Under Fasting Conditions and Corresponding Protein-Adjusted IQ_{95} Values

GS-9883 dose	N	Median (range) $C_{tau,SS}$ (ng/mL)	Median (range) $paIQ_{95}$[a]
5 mg	4	206.5 (146.0 – 342.0)	1.3 (0.9 – 2.1)
25 mg	4	797.5 (714.0 – 1900.0)	4.9 (4.4 – 12)
50 mg	4	2170.0 (852.0 – 3020.0)	13 (5.3 – 19)
100 mg	4	4190.0 (3730.0 – 5970.0)	26 (23 – 37)

a The $paIQ_{95}$ value is estimated based on steady-state C_{tau} values and the in vitro $paIC_{95}$ value for wild-type HIV-1 (162 ng/mL).
Source: Data on File

Single-agent GS-9883 was well tolerated at all doses administered. The range of GS-9883 plasma exposure at steady state ($C_{tau,SS}$) observed in the 50-mg cohort correlated with protein adjusted 95% inhibitory quotient ($paIQ_{95}$) values ranging from 5.3 to 19, while the range of GS-9883 plasma exposure at steady state ($C_{tau,SS}$) observed in the 100-mg cohort correlated with $paIQ_{95}$ values ranging from 23 to 37 (Table 1-5).

Based on PK/PD analyses, exposure following a 75-mg dose of single-agent GS-9883 is expected to provide near-maximal virologic response, with a predicted $paIQ_{95}$ of approximately 20, providing considerable coverage above the target concentration of 162 ng/mL ($paIC_{95}$). GS-9883 (75 mg) single agent coadministered with F/TAF (200/25 mg) is currently being evaluated in a Phase 2 study, GS-US-141-1475 (GS-9883+F/TAF vs DTG+F/TAF). The Week 24 data from this study support the safety and efficacy of GS-9883 exposures obtained with the 75 mg dose of the single agent.

GS-9883/F/TAF FDC Dose Selection

A fixed dose formulation of GS-9883/F/TAF was developed for use in Phase 3 studies. Preliminary results from the relative bioavailability (rBA) study (GS-US-141-1233) of GS-9883/F/TAF (75/200/25 mg) showed that GS-9883 plasma exposure was higher (with C_{max} and AUC_{inf} increase of 31% and 27%, respectively) following administration of the FDC as compared with exposure following administration of GS-9883 (75 mg) + F/TAF (200/25 mg) under fasted conditions. The increase in GS-9883 exposures associated with the FDC formulation results in an estimated mean $paIQ_{95}$ of 24.3, compared to an estimated mean $paIQ_{95}$ of 19.2 for the GS-9883 (75 mg) single agent coadministered with F/TAF, in the fasted state.

In order to bridge exposures of GS-9883 in the FDC to the exposure observed with GS-9883 75 mg administered as a single agent, and to bridge to the safe and effective exposures observed in the Phase 2 study GS-US-141-1475, a lower strength GS-9883/F/TAF FDC was developed for use in the Phase 3 studies. Comparability of GS-9883 exposures was confirmed in an rBA study of GS-9883/F/TAF (50/200/25 mg) and GS-9883 (75 mg) + F/TAF prior to initiation of dosing in the Phase 3 studies.

1.10. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the efficacy of switching from a regimen of DTG and ABC/3TC or a fixed dose combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF versus continuing DTG and ABC/3TC as the FDC ABC/DTG/3TC in virologically suppressed HIV-1 infected subjects as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48

The secondary objectives of this study are:

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

3. STUDY DESIGN

3.1. Endpoints

The primary efficacy endpoint is:

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

The secondary endpoints of this study include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count at Week 48
- The percentage change from baseline in hip and spine BMD at Week 48

3.2. Study Design

This protocol describes a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of switching to GS-9883/F/TAF FDC versus continuing DTG + ABC/3TC as the FDC ABC/DTG/3TC in HIV-1 infected subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen (of DTG + ABC/3TC or the FDC ABC/DTG/3TC) for ≥ 3 months prior to screening.

3.3. Study Treatments

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

Treatment Group 1: FDC of GS-9883 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) + Placebo to match FDC of abacavir 600 mg/ dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) administered orally, once daily, without regard to food (n=260)

Treatment Group 2: FDC of abacavir 600 mg/dolutegravir 50 mg/ lamivudine 300 mg (ABC/DTG/3TC) QD + Placebo to match FDC of GS-9883 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) administered orally, once daily, without regard to food (n=260)

3.4. Duration of Treatment

Subjects will be treated for at least 48 weeks during the blinded treatment phase. After Week 48, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit. Once the last subject completes the Week 48 visit and

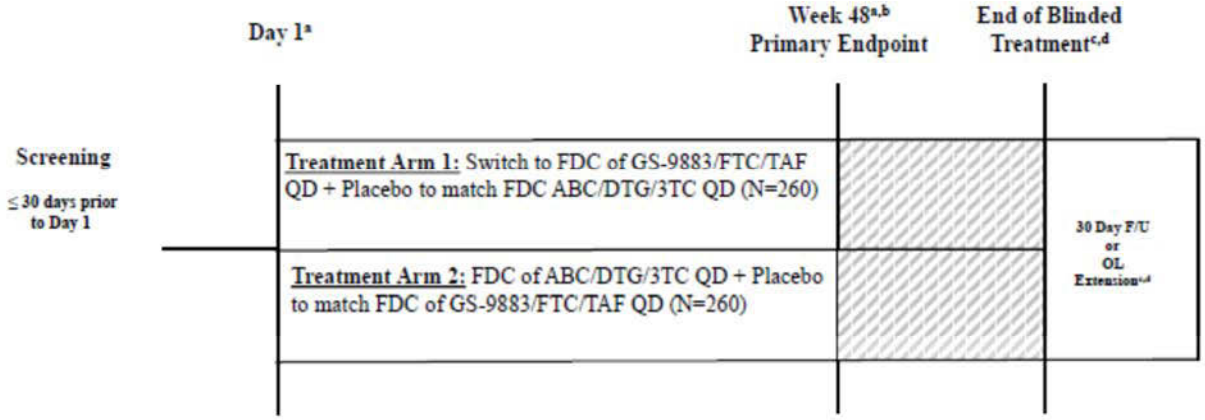
Gilead completes the Week 48 analysis, all subjects will return to the clinic (preferable within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of GS-9883/F/TAF is demonstrated following review of unblinded data, subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC in an open label extension phase for up to 96 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

All subjects participating in the open label extension phase, without regard to their blinded treatment regimen, will return for study visits at Week 12 OL and every 12 weeks thereafter for up to 96 weeks.

Subjects who complete the study through the End of Blinded Treatment Visit and do not continue on the open-label GS-9883/F/TAF FDC extension phase, will be required to return to the clinic 30 days after the End of Blinded Treatment visit for a 30-Day Follow-Up Visit.

Treatment assignments will be provided to the investigators within 30 days of the last subject completing the End of Blinded Treatment Visit.

Figure 3-1. Study Schema



a. Following the Day 1 visit, subjects will be required to return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Week 48.
b. After Week 48, subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit.
c. Once the last subject completes the Week 48 visit and Gilead completes the Week 48 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of GS-9883/F/TAF is demonstrated following review of unblinded data, subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC in an open-label extension for up to 96 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.
d. Subjects who complete the study through the End of Blinded Treatment Visit and do not continue on the open-label GS-9883/F/TAF FDC extension phase will be required to return to the clinic 30 days after the completion of study drugs for a 30-Day Follow-Up Visit.

3.5. Biomarker Testing

3.5.1. Biomarker Samples for Optional Pharmacogenomic Research

A separate, specific signature will be required to document a subject's agreement to provide additional samples for optional pharmacogenomic research. Pharmacogenomics is the study of how a person's genes affect a person's response to drugs. Genetic discovery research may identify or validate genetic markers that may be predictive of the safety and/or tolerability of study drugs used in this protocol.

For subjects who agree to participate and provide their additional specific consent, three blood samples will be obtained for the extraction of DNA for potential genomic testing and for genotyping to identify polymorphisms of drug metabolism enzymes including UGT1A1 and other biomarker research such as HLA. These samples will be collected at Day 1.

Subjects are not required to consent for optional pharmacogenomic research in order to participate in this study and have the right to withdraw their consent for optional pharmacogenomic research at any time and for any reason.

The sample consented for optional pharmacogenomic research will be destroyed 15 years after the end of the study.

3.5.2. Additional Sample Storage

For subjects who provide additional consent, residual blood and urine samples taken throughout the study will be stored. Stored samples may be used by the Sponsor or its research partners to help answer questions about the study drug, and HIV disease and its associated conditions, or to provide additional safety data. At the conclusion of this study, these samples may be retained in storage by Gilead Sciences for a period up to 15 years.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 520 subjects who meet the eligibility criteria will be enrolled.

4.2. Inclusion Criteria

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

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

2) Age ≥ 18 years

3) Currently receiving an antiretroviral regimen of DTG + ABC/3TC, or ABC/DTG/3TC FDC for ≥ 3 months prior to the screening visit

4) HIV RNA < 50 copies/mL at the screening visit

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

6) Adequate renal function:
   Estimated glomerular filtration rate ≥ 50 mL/min (≥ 0.83 mL/sec) according to the Cockcroft-Gault formula {Cockcroft et al 1976}:

   a) Male:

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

$$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in umol/L}) \times 0.6786} = \text{CLcr (mL/sec)}$$

   b) Female:

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

$$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in umol/L}) \times 0.6786} \times 0.85 = \text{CLcr (mL/sec)}$$

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

8) Total bilirubin ≤ 1.5 mg/dL (≤ 26 umol/L), or normal direct bilirubin

9) Adequate hematologic function (absolute neutrophil count ≥ 750/mm^3 (≥ 0.75 GI/L); platelets ≥ 50,000/mm^3 (≥ 50 GI/L); hemoglobin ≥ 8.5 g/dL (≥ 85 g/L))

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

11) Females of childbearing potential must agree to utilize protocol recommended highly effective contraceptive methods or be non-heterosexually active or practice sexual abstinence (as defined in Appendix 7) from screening, throughout the duration of the study period, and for 30 days following the last dose of study drug.

    a) Female subjects who utilize hormonal contraceptive as one of their birth control methods must have used the same method for at least 3 months prior to study drug dosing.

12) Male subjects who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception (as described in Appendix 7) throughout the study period and for 90 days following the last dose of study drug.

13) Male subjects must agree to refrain from sperm donation from first study drug dose until at least 90 days following the last study drug dose

14) Life expectancy ≥ 1 year

15) Currently on a stable regimen for ≥ 3 months preceding the screening visit with documented plasma HIV-1 RNA < 50 copies/mL for ≥ 3 months preceding the Screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL).

    Prior changes in antiretroviral regimen are only allowed due to tolerability issues or for regimen simplification. Unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or "blip") prior to screening are acceptable. If the lower limit of detection of the local HIV-1 RNA assay is <50 copies/mL (eg, <20 copies/mL), the plasma HIV-1 RNA level cannot exceed 50 copies/mL on two consecutive HIV-1 RNA tests.

16) Have no documented or suspected resistance to FTC, TFV, DTG, ABC or 3TC including, but not limited, to the reverse transcriptase resistance mutations K65R and M184V/I

4.3. Exclusion Criteria

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

1) An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening (refer to Appendix 6)

2) Subjects experiencing decompensated cirrhosis (e.g, ascites, encephalopathy, or variceal bleeding)

3) Have been treated with immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening, or expected to receive these agents or systemic steroids during the study (e.g, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies)

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

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

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

7) Participation in any other clinical trial, including observational studies, without prior approval from the sponsor is prohibited while participating in this trial

8) 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 the dosing requirements

9) Any known allergies to the excipients of GS-9883/F/TAF FDC or ABC/DTG/3TC FDC tablets

10) Females who are pregnant (as confirmed by positive serum pregnancy test)

11) Females who are breastfeeding

12) Subjects receiving ongoing therapy with any of the following medications in the table below, including drugs not to be used with FTC, TAF, GS-9883, DTG, ABC and 3TC

Drug Class	**Agents Disallowed***
Antiarrhythmic Agent	Dofetilide
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antimycobacterials	Rifampin, Rifapentine
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen
GI Motility Agents	Cisapride
Herbal/Natural Supplements	St. John's Wort, Echinacea

* 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.

13) Acute hepatitis in the 30 days prior to study entry

14) Chronic Hepatitis B Virus (HBV) infection, as determined by either:

    a) Positive HBV surface antigen and negative HBV surface antibody, regardless of HBV core antibody status, at the screening visit

    b) Positive HBV core antibody and negative HBV surface antibody, regardless of HBV surface antigen status, at the screening visit

15) Active tuberculosis infection

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

Subjects will be assigned a screening number at the time of consent. **Randomization and Day 1 visits cannot occur until subject eligibility has been confirmed.**

Once eligibility has been confirmed and prior to or during the Day 1, visit the Investigator or designee will randomize the subject using the Interactive Web Response System (IWRS). Once a subject number has been assigned to a subject, it will not be reassigned to any other subject. The subject number assignment and randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed.

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

The IWRS will assign study drug bottle numbers of blinded FDC of GS-9883/F/TAF + Placebo to match FDC of ABC/DTG/3TC, or FDC of ABC/DTG/3TC + Placebo to match FDC of GS-9883/F/TAF at each study visit for each subject.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IWRS system for that subject. Gilead strongly recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Drug Safety and Public Health (DSPH) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling

5.2.1. Formulation

5.2.1.1. GS-9883/Emtricitabine/Tenofovir alafenamide (GS-9883/F/TAF) 50 mg/200 mg/25 mg and Placebo to Match Tablets

GS-9883 50 mg/Emtricitabine 200 mg/Tenofovir alafenamide 25 mg tablets are capsule-shaped, film-coated purplish-brown, debossed with "GSI" on one side of the tablet and "9883" on the other side of the tablet. Each tablet core contains 50 mg of GS-9883, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide. In addition to the active ingredients, the GS-9883/F/TAF tablets contain croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet cores are film-coated with iron oxide red, iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

The placebo to match (PTM) GS-9883/F/TAF tablets are capsule-shaped, film-coated purplish-brown, debossed with "GSI" on one side of the tablet and "9883" on the other side and are identical in physical appearance to GS-9883/F/TAF tablets. The placebo tablets contain microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate. The tablet cores are film-coated with iron oxide red, iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

5.2.1.2. Abacavir/Dolutegravir/Lamivudine (ABC/DTG/3TC Triumeq®) 600 mg/50 mg/300 mg and Placebo to Match Tablets

Abacavir 600 mg/Dolutegravir 50 mg/Lamivudine 300 mg tablets are oval, film coated purple, and debossed with “572 Tri” on one side. Each tablet core contains 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine. In addition to the active ingredients, the ABC/DTG/3TC tablets contain the inactive ingredients D-mannitol, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet cores are film coated with iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium oxide.

The PTM ABC/DTG/3TC tablets are oval, film coated purple, and debossed with “572 Tri” on one side. The placebo tablets are identical in physical appearance to ABC/DTG/3TC tablets. The placebo tablets contain microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate. The tablet cores are film-coated with iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium oxide.

5.2.2. Packaging and Labeling

5.2.2.1. GS-9883/Emtricitabine/Tenofovir alafenamide (GS-9883/F/TAF) 50 mg/200 mg/25 mg and Placebo to Match Tablets

GS-9883/F/TAF tablets and PTM GS-9883/F/TAF tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

5.2.2.2. Abacavir/Dolutegravir/Lamivudine (ABC/DTG/3TC Triumeq®) 600 mg/50 mg/300 mg and Placebo to Match Tablets

ABC/DTG/3TC tablets and PTM ABC/DTG/3TC tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and silica gel desiccant. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

5.2.3. Storage and Handling

Study drug GS-9883/F/TAF FDC, ABC/DTG/3TC FDC and placebo-to-match tablets for both FDCs 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(s) 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 GS-9883/Emtricitabine/Tenofovir alafenamide and Abacavir/Dolutegravir/Lamivudine

Study drug GS-9883/F/TAF FDC, ABC/DTG/3TC FDC and placebo-to-match tablets for both FDCs will be provided by Gilead Sciences.

Treatment Group 1: FDC of GS-9883 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) + Placebo to match FDC of abacavir 600 mg/ dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) administered orally, once daily, without regard to food

Treatment Group 2: FDC of abacavir 600 mg/dolutegravir 50 mg/ lamivudine 300 mg (ABC/DTG/3TC) + Placebo to match FDC of GS-9883 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) administered orally, once daily, without regard to food

After the End of Blinded Treatment Visit, all subjects who choose to participate in the open-label extension will receive GS-9883/F/TAF FDC once daily for up to 96 weeks.

Subjects will be instructed to bring all study medication in the original container at each clinic visit for drug accountability. The Investigator will be responsible for maintaining accurate records for all study drug bottles dispensed and tablets returned. The inventory and dispensing logs must be available for inspection by the study monitor. Study medication supplies, including partially used or empty bottles, must be accounted for by the study monitor prior to destruction or return.

5.4. Prior and Concomitant Medications

- The use of medications for the treatment of HIV, other than study drug, is prohibited.
- Medications listed in the following table and use of herbal/natural supplements are excluded or should be used with caution while subjects are participating in the study. Subjects will refrain from consumption of grapefruit juice and Seville orange juice throughout participation in the study.

Table 5-1. Prior and Concomitant Medications

Drug Class	Agents Disallowed*	Use Discouraged and To Be Used With Caution
Acid Reducing Agents Antacids Buffered medications		Concentration of study drug may decrease with antacids. Subjects may not take antacids (eg, Tums or Rolaids); the ulcer medication sucralfate (Carafate); or vitamin or mineral supplements that contain calcium, iron or zinc for a minimum of 6 hours before and 2 hours after any dose of study drug.
Antiarrhythmic Agent	Dofetilide	
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials	Rifampin, Rifapentine	
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen	
GI Motility Agents	Cisapride	
Herbal/Natural Supplements	St. John's Wort, Echinacea	
Oral Hypoglycemic Agent		Metformin: close monitoring is recommended. A dose adjustment of Metformin may be necessary. Limit total daily doses of Metformin to 1000mg when initiating study medication or if initiating metformin while on study drug.

* 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.

Should subjects have a need to initiate treatment with any excluded 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 excluded medication.

5.5. Accountability for Investigational Medicinal Product (IMP)

The investigator is responsible for ensuring adequate accountability of all used and unused IMP. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP dispensed to subjects must be returned to the site.

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

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

5.5.1. Investigational Medicinal Product Return or Disposal

Study drug return and disposal will be performed as outlined in Section 9.1.7.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2, Appendix 3 and described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible for study prior to enrollment. Please refer to Section 6.2.2 for details about randomization and treatment assignment.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

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

- Obtain written informed consent
- Obtain medical history including history of HIV-1 disease-related events, smoking 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)
- 12-lead ECG performed supine
- Height
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Urine collection for the following laboratory procedures:
  - Urinalysis
- Blood sample collection for the following laboratory analyses:
  - Serum pregnancy test (females of childbearing potential only). If the test is positive, the subject will not be enrolled

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

— Estimated glomerular filtration rate according to the Cockcroft-Gault formula:

■ Male:

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

$$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in umol/L}) \times 0.6786} = \text{CLcr (mL/sec)}$$

■ Female:

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

$$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in umol/L}) \times 0.6786} \times 0.85 = \text{CLcr (mL/sec)}$$

— 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 B surface antibody (HBsAb)

— Hepatitis B virus core antibody (HBcAb)

— Hepatitis C virus (HCVAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed.

- Review of adverse events and concomitant medications

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30-days after screening for Day 1 Visit into the study. Subjects must continue to take their prior treatment regimen up until their scheduled Day 1 visit.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Day 1 Assessments

The following evaluations are to be completed at the Day 1 Visit. **The Investigator must have confirmed eligibility before proceeding with the Day 1 visit.** The subject must complete all study procedures, except DXA, before being administered the study drug:

- DXA Scan (spine and hip). For subjects in Germany, DXA scans will not be performed.
  - The DXA scan will be performed on subjects once eligibility is confirmed. The scan may be performed prior to or within 24 hours of 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 measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- 12-lead ECG performed supine
- Short Form 36 Health Survey (SF-36), HIV Symptoms Distress Module, Work Productivity and Activity Impairment Questionnaire (WPAI) and Pittsburgh Sleep Quality Index (PSQI) to be completed by the subject. Subject is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2 microglobulin
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will not be able to participate
  - Urine storage sample for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) and TSH

  - Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Plasma HIV-1 RNA
  - CD4+ cell count
  - Evaluations of inflammation and immune activation, may include but not limited to cystatin C, IL-6, hs-CRP, d-dimer, sCD14 and sCD163
  - Evaluations of platelet function, may include but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand.
  - Plasma storage sample for safety, virology, or PK testing
  - Whole blood sample for potential HIV DNA genotyping
- **Optional blood sample collection for the following laboratory analyses if pharmacogenomics consent is obtained**
  - Whole blood/EDTA for HLA testing, UGT1A1 testing and additional biomarker testing
- Provide subject dosing diary to all subjects
- Dispense study drug
- Observed first dose administration of the assigned study drugs as described in Section 5.3
- Subjects should be instructed to take study drugs without regard to food. The subject should be counseled regarding the importance of adherence and taking their study medications at approximately the same time each day as directed by the Investigator.

6.3. Randomization

Once eligibility has been confirmed and prior to or during the Day 1 visit, the Investigator or designee will randomize the subject using the Interactive Web Response System (IWRS). Once a subject number has been assigned to a subject, it will not be reassigned to any other subject. The subject number assignment and randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed.

6.4. Treatment Assessments (Week 4 - 48)

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

Study visits are to be completed within ± 2 days of the protocol-specified visit date based on the Day 1 visit through Week 12 and completed within ± 6 days of the protocol-specified visit date through Week 36, unless otherwise specified. The visit window at Week 48 will be ± 6 weeks of the protocol-specified visit date, and these clinical visit windows coincide with the Week 48 statistical analysis window for HIV-1 RNA.

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

- Review of AEs and changes in concomitant medications
- DXA scans (spine and hip) for all subjects who are on study drug **(Weeks 24 and 48 ±10 days).** For subjects in Germany, DXA scans will not be performed.
- Complete physical examination **(Weeks 24 and 48)** (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- 12-lead ECG performed supine **(Weeks 24 and 48)**
- Short Form 36 Health Survey (SF-36), HIV Symptoms Distress Module, Work Productivity and Activity Impairment Questionnaire (WPAI) and Pittsburgh Sleep Quality Index (PSQI) to be completed by the subject at **Weeks 4, 12 and 48**. Subject is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2 microglobulin. **(Weeks 24 and 48)**
  - 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 storage sample for possible additional clinical testing

- Blood sample collection for the following laboratory analyses:

  — Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). At Weeks 12, 24 and 48, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. At Weeks 24 and 48, TSH will also be analyzed.

  — 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 12, 24, and 48)**

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

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

  — Plasma HIV-1 RNA

  — CD4+ cell count

  — Evaluations of inflammation and immune activation, may include but not limited to cystatin C, IL-6, hs-CRP, d-dimer, sCD14 and sCD163 **(Weeks 24 and 48)**

  — Evaluations of platelet function, may include but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand **(Weeks 24 and 48)**

  — Hepatitis B virus surface antigen serology (HBsAg). Subjects who have HBVsAg positive will have a reflex test for HBV DNA (viral load). **(Week 48)**

  — Hepatitis B surface antibody (HBsAb) **(Week 48)**

  — Hepatitis B virus core antibody (HBcAb) **(Week 48)**

  — Hepatitis C virus (HCVAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed. **(Week 48)**

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

- Pharmacokinetic Blood Collection for subjects who are on study drug. Details of pharmacokinetic blood sampling procedures and sample management will be documented in the Pharmacokinetic Sample Collection, Processing, Storage, and Shipment Manual.

  — **Single Anytime, Trough and Post Dose PK Sample for all Subjects on Study Drug:**

    - Subjects will have a single anytime pre or post-dose PK blood sample at **Weeks 8, 24 and 36**.

    - Observed dosing at the clinic: Subjects will have a trough PK blood sample collected between 20-28 hours following their last dose at **Weeks 4 and 12.** Subjects must be instructed to not take their study drugs on the morning of their visit for the trough sample collection. Subjects will then take an observed dose of study drug at the clinic. A single post dose PK blood sample will be collected between 1 and 4 hours post dose. If the subject has taken their dose of study drugs prior to the visit, the visit may proceed, but the subject must return within 72 hours for the trough PK blood sample collection. In the event a subject routinely takes their study drug in the evening, a single post dose sample may be drawn at Weeks 4 and 12 as the subject will not be instructed to change their dosing time to accommodate this trough PK draw.

    - Dosing diaries will be collected from subjects for the single anytime PK and trough PK collection. If a dosing diary is not returned the site may ask the subject for the time of the last dose and if it was taken with or without food.

  — **Optional Pharmacokinetic (PK) Substudy:**

    - A PK substudy will be performed at the Week 4 or 8 visit in a subset of subjects (approximately n=30 evaluable) at selected study sites. The substudy will include intensive PK profiling in plasma.

    - Observed dosing at the clinic: At the Week 4 or 8 visits subjects will be asked to return to the clinic 20-28 hours after their previous dose for a trough PK blood sample collection. Subjects must be instructed to not take their study drugs on the morning of their visit for the trough sample collection. Subjects will then take an observed dose of study drug at the clinic. Additional blood samples will be collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 hrs post-dose. If the subject comes to clinic on the PK substudy day and has already taken his/her dose of study drugs prior to the visit, the visit may proceed but not the PK substudy. In this case, the subject must return within 72 hours, having not taken their dose of study drugs on the morning of the returning day on Week 4 or 8 in order to participate.

    - Subject dosing diaries will be collected from PK substudy subjects.

- Provide subject dosing diary to all subjects. **(Weeks 4, 8, 12 and 24)**

- Document study drug dispensation and accountability for all study drugs dispensed.
- Subjects who meet the criteria for virologic failure will be managed according to the Management of Virologic Rebound Sections 6.13.1 and 6.13.2.

6.5. Treatment Assessments (Post Week 48 until the Open-Label Rollover Extension)

6.5.1. Post Week 48 Assessments

After Week 48, all subjects will continue to take their blinded study drugs and attend visits every 12 weeks until the End of Blinded Treatment Visit. Once the last subject completes the Week 48 visit and Gilead completes the Week 48 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. Study visits are to be completed within ± 6 days of the protocol-specified visit date unless otherwise specified.

- Review of AEs and changes in concomitant medications
- Complete physical examination **(Every 48 weeks)** (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- 12-lead ECG performed supine **(Every 48 weeks)**
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2 microglobulin. **(Every 24 weeks)**
  - 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 storage sample for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). Every 24 weeks, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. In addition, TSH will also be analyzed every 24 weeks.

- — Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments. **(Every 24 weeks)**
- — Estimated glomerular filtration rate according to the Cockcroft-Gault formula
- — Hematology profile: complete blood count (CBC) with differential and platelet count
- — Plasma HIV-1 RNA
- — CD4+ cell count
- — Evaluations of inflammation and immune activation, may include but not limited to cystatin C, IL-6, hs-CRP, d-dimer, sCD14 and sCD163 **(Every 24 weeks)**
- — Evaluations of platelet function, may include but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand **(Every 24 weeks)**
- — Hepatitis B virus surface antigen serology (HBsAg). Subjects who have HBVsAg positive will have a reflex test for HBV DNA (viral load). **(Every 48 weeks)**
- — Hepatitis B surface antibody (HBsAb) **(Every 48 weeks)**
- — Hepatitis B virus core antibody (HBcAb) **(Every 48 weeks)**
- — Hepatitis C virus (HCVAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed. **(Every 48 weeks)**
- — Plasma storage sample for safety, virology, or PK testing

- Document study drug dispensation and accountability for all study drugs dispensed.
- Subjects who meet the criteria for virologic failure will be managed according to the Management of Virologic Rebound Sections 6.13.1. and 6.13.2

6.5.2. End of Blinded Treatment Visit

Once the last subject completes the Week 48 visit and Gilead completes the Week 48 analysis, all subjects will return to the clinic (preferably within 30 days)) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of GS-9883/F/TAF is demonstrated following review of unblinded data, subjects in a country where GS-9883/F/TAF FDC is not available, will be given the option to receive GS-9883/F/TAF FDC in an open-label extension phase for up to 96 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

Subjects who receive the open-label GS-9883/F/TAF FDC will return for study visits every 12 weeks.

Subjects who choose to not receive the open-label GS-9883/F/TAF FDC will be required to return to the clinic for a 30-Day Follow-up visit following the End of Blinded Treatment Visit. Subjects who have discontinued drug study prior to the End of Blinded Treatment Visit will not be eligible for the open-label rollover extension; these subjects will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Visit and discontinue the study after the End of Blinded Treatment Visit.

Treatment assignments will be provided to the investigators within 30 days of the last subject completing the End of Blinded Treatment Visit.

The following will be performed at the End of Blinded Treatment Visit:

- Review of AEs and changes in concomitant medications
- DXA scans (spine and hip) for all subjects who are on study drug **(±10 days)** if last scan was acquired > 12 weeks from the date of the End of Blinded Treatment Visit. For subjects in Germany, DXA scans will not be performed.
- 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), including weight
- 12-lead ECG performed supine
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2 microglobulin.
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will not be able to participate.
  - Urine storage sample for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN), and TSH

- — Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments
- — Estimated glomerular filtration rate according to the Cockcroft-Gault formula
- — Hematology profile: complete blood count (CBC) with differential and platelet count
- — Plasma HIV-1 RNA
- — CD4+ cell count
- — Evaluations of inflammation and immune activation, may include but not limited to cystatin C, IL-6, hs-CRP, d-dimer, sCD14 and sCD163
- — Evaluations of platelet function, may include but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand
- — Plasma storage sample for safety, virology, or PK testing

- Document study drug dispensation, if applicable, and accountability for all study drugs dispensed
- Subjects who wish to continue in the Open-Label Rollover Extension study will receive open-label GS-9883/F/TAF FDC.

6.5.3. Treatment Assessments (Open-Label Rollover Extension)

For purposes of study visit identification during the open-label rollover extension, study visits will be identified by the number of weeks that have elapsed between the End of Blinded Treatment Visit and the corresponding open-label study visit, and labeled with “OL” (eg. Week 12 OL, Week 24 OL, etc.).

All subjects participating in the open-label extension phase, without regard to their blinded treatment regimen, will return for study visits at Week 12 OL, and every 12 weeks thereafter for up to 96 weeks.

Study visits are to be completed within ± 6 days of the protocol-specified visit date based on the End of Blinded Treatment Visit date, unless otherwise specified.

The following will be performed at the Open-Label Extension Visits:

- Review of AEs and changes in concomitant medications

- Complete physical examination **(Weeks 48 OL and 96 OL)** (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed

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

- 12-lead ECG performed supine **(Weeks 48 OL and 96 OL)**

- Urine collection for the following laboratory procedures:

  — Urinalysis

  — 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 storage sample for possible additional clinical testing

- Blood sample collection for the following laboratory analyses:

  — Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). Every 24 weeks, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. In addition, TSH will also be analyzed every 24 weeks.

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

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

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

  — Plasma HIV-1 RNA

  — CD4+ cell count

  — Hepatitis B virus surface antigen serology (HBsAg)**.** Subjects who have HBVsAg positive will have a reflex test for HBV DNA (viral load). **(Weeks 48 OL and 96 OL)**

— Hepatitis B surface antibody (HBsAb) **(Weeks 48 OL and 96 OL)**

— Hepatitis B virus core antibody (HBcAb) **(Weeks 48 OL and 96 OL)**

— Hepatitis C virus (HCVAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed. **(Weeks 48 OL and 96 OL)**

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

- Document study drug dispensation and accountability for all study drugs dispensed.
- Subjects who meet the criteria for virologic failure will be managed according to the Management of Virologic Rebound Sections 6.13.1. and 6.13.2

6.6. Post-treatment Assessments

6.6.1. Early Study Drugs Discontinuation Assessments

If the subject discontinues study drug prior to the End of Blinded Treatment Visit, the subject will be asked to return to the clinic within 72 hours of stopping study drugs for the Early Study Drugs Discontinuation Visit. The subject will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Visit.

If the subject discontinues study drug during the Open-Label Rollover Extension, the subject will be asked to return to the clinic within 72 hours of stopping the study drug for the Early Study Drugs Discontinuation Visit.

At the Early Study Drugs Discontinuation Visit, any evaluations showing abnormal results indicating that <u>there is a possible or probable causal relationship with the study drug</u>, 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 Drugs Discontinuation Visit:

- Review of AEs and changes in concomitant medications
- DXA scan required (spine and hip) for all subjects who are on study drug **(±10 days**) if last scan was acquired > 12 weeks from the date of the ESDD Visit (blinded treatment phase only). For subjects in Germany, DXA scans will not be performed.
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- 12-lead ECG performed supine (blinded treatment phase only)

- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test
  - Urine storage sample for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN), and TSH
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Plasma HIV-1 RNA
  - CD4+ cell count
  - Plasma storage sample for safety, virology, or PK testing
  - HIV-1 genotype/phenotype testing for subjects with virologic failure
- Drug accountability

6.6.2. 30 Day Follow Up

Subjects who complete the study drug through the End of Blinded Treatment visit and who do not wish to participate in the open-label rollover extension, will be required to return to the clinic 30 days after the completion of study drug for the 30 Day Follow Up visit.

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

Those subjects who prematurely discontinue study drug during the blinded phase and continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit will not be required to complete the 30-Day Follow-Up Visit.

Subjects who prematurely discontinue study drug during the Open-Label Rollover Extension will be asked to return to the clinic 30 days after the completion of the Early Study Drugs Discontinuation Visit for the 30-day Follow-Up Visit. The subject will not continue attending the scheduled study visits.

Subjects who complete the Open-Label Rollover Extension will be asked to return to the clinic 30 days after the completion of study drugs for the 30-day Follow-Up Visit.

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

- Review of AEs and changes in concomitant medications
- Symptom-directed physical examination
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test.
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN).
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula
  - Hematology profile: complete blood count (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 drugs 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.

6.7. Criteria for Discontinuation of Study Treatment

Study medication will be discontinued in the following instances:

- 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
- Subject request to discontinue for any reason
- Pregnancy during the study; refer to Appendix 7
- Development of active tuberculosis infection

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator
- Lack of efficacy
- Subject noncompliance
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.8. Bone Mineral Density Evaluations

For all subjects who are on study drug, excluding those enrolled in sites based in Germany, dual energy x-ray absorptiometry (DXA) scans will be performed prior to or within 24 hours of Day 1, Weeks 24, 48, End of Blinded Treatment Visit and the Early Study Drug Discontinuation Visit (if the last scan was acquired > 12 weeks from the date of the ESDD Visit) during the blinded treatment phase. Scans will cover the spine and hip to measure changes in bone mineral density. DXA scan results will be provided to study sites.

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

6.9. Other Evaluations

6.9.1. Markers of Renal Tubular Function

For all subjects, urine will be collected for selected evaluations of renal tubular function, which will include urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2 microglobulin at Day 1 Visit, Weeks 24, 48, every 24 weeks post Week 48, and the End of Blinded Treatment Visit. Samples may be stored for a period of 15 years at the end of the

study.

6.9.2. Markers of Inflammation and Immune Activation

For all subjects, blood will be collected at Day 1 Visit, Weeks 24, 48, every 24 weeks post Week 48, and the End of Blinded Treatment Visit for selected evaluations of inflammation and immune activation, which may include but not limited to cystatin C, IL 6, hs CRP, d-dimer, sCD14, and sCD163. Samples may be stored for a period of 15 years at the end of the study.

6.9.3. Markers of Platelet Function

For all subjects, blood will be collected at Day 1 Visit, Weeks 24, 48, every 24 weeks post Week 48, and the End of Blinded Treatment Visit for selected evaluations of platelet function, which may include but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand. Samples may be stored for a period of 15 years at the end of the study.

6.9.4. Blood and Urine Storage

A portion of the blood and urine samples drawn at all visits (except the Screening Visit, 30-day follow-up Visit and Unscheduled Visits) will be frozen and stored. These stored blood and urine samples may be used by the Sponsor or its research partners for HIV-1 genotyping/phenotyping assays or their development, for retesting the amount of HIV-1 in the blood, for measurement of antiviral drug levels in the blood, or for testing to learn more about how the study drug has worked against HIV-1 or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without expressed consent of study subjects. At the conclusion of this study, these samples may be retained in storage by Gilead Sciences for a period up to 15 years.

6.10. 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 and continue to perform the required study-related follow-up and procedures (see Section 6.7, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.11. End of Study

The end of study will be the last patient's last observation (or visit).

6.12. Post Study Care

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

6.13. Virologic Failure

Virologic failure is defined as virologic rebound or having HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation, or Week 48.

6.13.1. Management of Virologic Rebound

Subjects who meet the criteria listed below will be considered to have virologic rebound:

- At any post Day 1 visit, a rebound in HIV-1 RNA ≥ 50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit; OR
- Any subject with HIV RNA ≥ 50 copies/mL at study drug discontinuation

Following the unconfirmed virologic rebound, subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after the date of the original test that resulted in HIV-1 RNA virologic rebound) for confirmation of virologic rebound. If virologic rebound is confirmed at the scheduled or unscheduled visit and the HIV-1 RNA is ≥ 200 copies/mL, the blood sample from the confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing. Subjects with documented non-adherence within 72 hours of the visit may not be tested for resistance. After a subject's first post-baseline resistance test, additional testing will be conducted on a case-by-case basis. Any subject may be discontinued at Investigator's discretion or per local treatment guidelines.

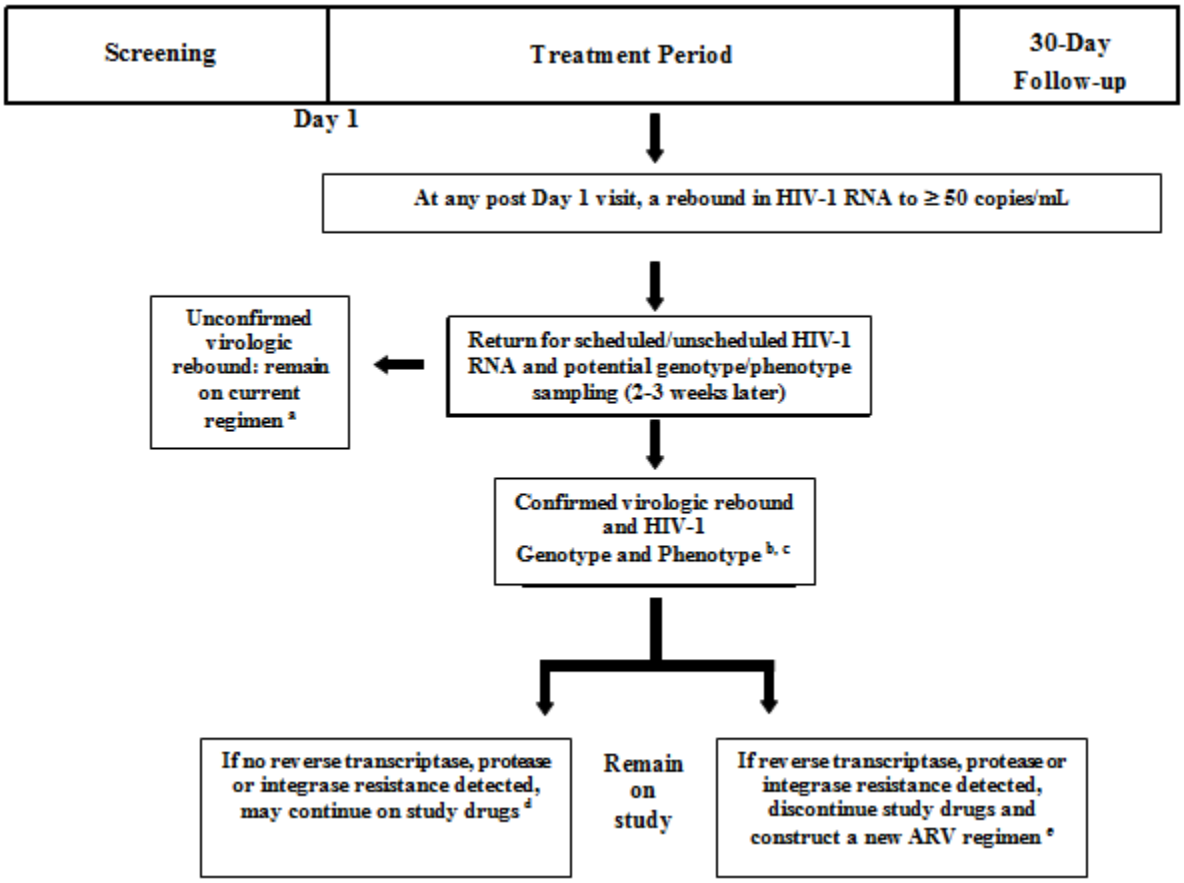
If no resistance is detected from the genotype or phenotype, the subject may remain on study drugs and HIV-1 RNA test should be repeated (2 to 3 weeks after date of test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug for each individual subject and document this assessment in the on-site medical record.

Subjects who are noncompliant on an ongoing basis will be considered for discontinuation per the Investigator's discretion or local treatment guidelines. Investigators who opt to discontinue study drugs for an individual subject must discuss with the Medical Monitor prior to study drug discontinuation.

For subjects who are off study drug but remain on study, it will be the Investigator's discretion to manage virologic rebound.

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

Figure 6-1. Virologic Rebound Schema



a. If virologic rebound is not confirmed, the subject will remain on their current regimen.
b. If virologic rebound is confirmed and the HIV-1 RNA is ≥ 200 copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase) will be analyzed.
c. Based on the results of the genotypic and phenotypic assays, the subject will remain on study drugs or study drugs will be discontinued. If genotyping or phenotyping fails, a new ARV regimen may be configured at the discretion of the Investigator.
d. If no resistance is detected, HIV-1 RNA will be repeated (2-3 weeks later). Investigator reviews study drug continuation/discontinuation options and discusses with the Medical Monitor prior to study drug discontinuation
e. A new ARV regimen will be configured, at the Investigator's discretion, and the subject will remain in the study.

6.13.2. Subjects with HIV-1 RNA ≥ 50 copies/mL at Study Drug Discontinuation, or Week 48

Subjects with HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation or last visit will be considered virologic failures. Subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 will be asked to return for an unscheduled visit within the visit window for a retest.

Subjects with HIV-1 RNA ≥ 200 copies/mL at study drug discontinuation, last visit or Week 48, will also have resistance testing conducted.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

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

7.1.2. Serious Adverse Events

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

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- No: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- Yes: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

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

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

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

7.2.2. Assessment of Severity

AE severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 5). For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

The distinction between the seriousness and the severity of an adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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

Requirements for collection prior to study drug initiation:

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

- all SAEs and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

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

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

7.3.2. Serious Adverse Events

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

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

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

<u>Electronic Serious Adverse Event (eSAE) Reporting Process</u>

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

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

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

- 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.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form

- 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.

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, EU Summary of Product Characteristics (SmPC), or relevant local label as applicable.

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

7.5. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 4 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 5)

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

- Any questions regarding toxicity management should be directed to the Gilead 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, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product will be withheld until the toxicity returns to ≤ Grade 2. When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose upon discussion with the Gilead Sciences Medical Monitor.
- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product will be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation but requires discussion with the Gilead Sciences 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 investigational medicinal product, investigational medicinal product will be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.
- Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 CK after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product requires discussion with the Gilead Sciences Medical Monitor.

7.5.4. Management of Possible Abacavir Hypersensitivity Reaction

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

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

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

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

Regardless of their HLA-B*5701 status, patients who are diagnosed with a hypersensitivity reaction whilst on therapy MUST discontinue study drug immediately and MUST NEVER be restarted. Restarting study drug following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, study drug must be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medicinal products) {Ezzati et al 2003}.

7.5.5. Management of Potential Hepatobiliary Toxicity

Monkeys given a high dose (1000 mg/kg/day) for 39 weeks had evidence of biliary hyperplasia and hepatocyte hypertrophy on histopathologic examination. The risk to humans given the clinical dose of GS-9883 (50 mg/day) is unknown. Investigators should be aware of this potential toxicity. Any study subject exhibiting signs/symptoms or laboratory abnormalities suggestive of possible hepatobiliary toxicity should undergo thorough examination and clinical workup as deemed appropriate by the Investigator, and the Investigator must communicate promptly with the Gilead Medical Monitor. Consideration should be given to appropriate imaging studies (for example, ultrasound of the liver and biliary tree) and potential consultation with a gastroenterologist with specialty training in hepatobiliary diseases. Management of graded laboratory and clinical abnormalities will be managed as outlined in Section 7.5.

7.5.6. On-Treatment Hepatitis C Management

If a subject tests positive for HCV RNA at screening or develops signs or symptoms of active Hepatitis C virus Gilead recommends that local medical practice is followed at the discretion of the Investigator. Investigational medicinal product may be continued without dose interruption. Should the Investigator decide to initiate Hepatitis C treatment the Investigator must contact the Gilead Medical Monitor to confirm that no drug-drug interactions are expected.

Subjects should return to the clinic for scheduled or unscheduled follow up visit(s) according to local medical practice for laboratory evaluations. If Hepatitis C treatment is initiated, Investigators should use the Gilead provided retest laboratory kits to manage the active Hepatitis C.

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, reports of adverse reactions in infants following exposure from breastfeeding, occupational exposure with an adverse event, and pregnancy reports regardless of an associated AE.

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

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

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

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

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

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

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

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

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

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

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1 650 522-5477 or email Safety_FC@gilead.com.

Refer to Appendix 7 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 IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the efficacy of switching from a regimen of DTG and ABC/3TC or a FDC of ABC/DTG/3TC to a FDC of GS-9883/F/TAF versus continuing DTG and ABC/3TC as the FDC ABC/DTG/3TC in virologically suppressed HIV-1 infected subjects as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48

The secondary objectives of this study are:

- To evaluate the safety, and tolerability of the two treatment groups through Week 48
- To evaluate the bone safety of the two treatment groups as determined by the percentage change from baseline in hip and spine BMD through Week 48

8.1.2. Primary Endpoint

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

8.1.3. Secondary Endpoint

Secondary endpoints include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count at Week 48
- The percentage change from baseline in hip and spine BMD at Week 48

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized

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

8.2.1.2. Efficacy

8.2.1.2.1. Full Analysis Set (FAS)

The primary analysis set for efficacy analyses is defined as full analysis set (FAS), which will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of study drug. Subjects will be grouped according to the treatment to which they were randomized.

8.2.1.2.2. Per-Protocol (PP) Analysis Set

The secondary analysis set for efficacy analyses is defined as per-protocol (PP) analysis set, which will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have not committed any major protocol violation, including the violation of key entry criteria. Subjects will be grouped according to the treatment they actually received.

Subjects meeting any of the following criteria will be excluded from the Week 48 PP analysis set:

- Subjects who do not have on-treatment HIV-1 RNA in the Week 48 analysis window, except when missing is due to discontinuation of study drug for lack of efficacy.
- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the table in protocol Section 4.3 including drugs not to be used with GS-9883, FTC, TAF, ABC, 3TC, and DTG.
- Nonadherence to study drug: subjects with adherence rate for active study drug up to the Week 48 Visit below the 2.5th percentile

8.2.1.3. Safety

The primary analysis set for safety analyses is defined as safety analysis set, which will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of study drug. All the data collected up to 30 days after subjects permanently discontinue their study drug will be included in the safety summaries, unless specified otherwise. Subjects will be grouped according to the treatment they actually received.

8.2.1.4. Pharmacokinetics

8.2.1.4.1. Pharmacokinetic (PK) Substudy Analysis Set

The primary analysis set for intensive PK analyses is defined as the PK substudy analysis set, which will include all subjects who (1) are randomized into the study, (2) enrolled into the PK Substudy, (3) have received at least 1 dose of GS-9883/F/TAF, and (4) have at least 1 nonmissing intensive PK concentration data for any analyte of interest reported by the PK lab.

8.2.1.4.2. Pharmacokinetic (PK) Analysis Set

The primary analysis set for general PK analyses is defined as the PK analysis set, which will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of GS-9883/F/TAF, and (3) have at least 1 nonmissing PK concentration data for any analyte of interest reported by the PK lab.

8.2.1.5. DXA

8.2.1.5.1. Hip DXA Analysis Set

The primary analysis set for hip BMD analyses is defined as the Hip DXA analysis set, which will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have nonmissing baseline hip BMD value. Subjects will be grouped according to the treatment they actually received.

8.2.1.5.2. Spine DXA Analysis Set

The primary analysis set for spine BMD analyses is defined as the Spine DXA analysis set, which will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have nonmissing baseline spine BMD value. Subjects will be grouped according to the treatment they actually received.

8.3. Data Handling Conventions

HIV-1 RNA results of 'No HIV-1 RNA detected' and "<20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purpose.

Natural logarithmic transformation of plasma concentrations and PK parameters will be applied for PK analysis.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit plus or minus one significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed. However, a missing pre-treatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

All available data for subjects that do not complete the study will be included in data listings.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive methods including sample size, mean, SD, median, Q1, Q3, minimum, and maximum for continuous variables and frequency and percentages for categorical variables.

Demographic data will include sex, race, ethnicity, and age.

Baseline characteristics will include body weight, height, body mass index, eGFR, HIV-1 infection, and enrollment distribution will be summarized.

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

8.5. Efficacy Analysis

8.5.1. Primary Analysis

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

8.5.1.1. US FDA-defined Snapshot Algorithm

The analysis window at Week 48 is defined as from Study Day 295 to Study Day 378, inclusive. All HIV-1 RNA data collected on-treatment (ie, including data collected up to 1 day after the last dose date of study drug) will be used in the snapshot algorithm. Virologic outcome will be defined as the following categories:

- **HIV-1 RNA < 50 copies/mL**: this includes subjects who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 48 analysis window
- **HIV-1 RNA ≥ 50 copies/mL**: this include subjects
  - a) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 48 analysis window, or
  - b) Who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window and
    - 1) Who discontinue study drug prior to or in the Week 48 analysis window due to lack of efficacy, or
    - 2) Who discontinue study drug prior to or in the Week 48 analysis window due to reason other than lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL

- **No Virologic Data in the Week 48 Analysis Window**: this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window because of the following:

  a) Discontinuation of study drug prior to or in the Week 48 analysis window due to reasons other than lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL, or

  b) Missing data during the window but on study drug

8.5.1.2. Analysis of Primary Efficacy Endpoint

The null hypothesis is that the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 in the GS-9883/F/TAF group is at least 4% higher than that in the ABC/DTG/3TC group; the alternative hypothesis is that the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL in the GS-9883/F/TAF group is less than 4% higher than that in the ABC/DTG/3TC group.

Non-inferiority will be assessed using the conventional confidence interval (CI) approach. The point estimate of treatment difference (GS-9883/F/TAF – ABC/DTG/3TC) and the associated 2-sided 95% CI will be constructed based on the exact method.

It will be concluded that GS-9883/F/TAF is non-inferior to ABC/3TC/DTG if the upper bound of the 2-sided 95% CI of the difference between treatment groups (GS-9883/F/TAF - ABC/3TC/DTG) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL is less than 4%.

If non-inferiority of GS-9883/F/TAF to ABC/DTG/3TC is established, the upper bound of the 95% CI will be compared to 0; if the upper bound of the 95% CI is less than 0, superiority of GS-9883/F/TAF over ABC/DTG/3TC will be established.

8.5.2. Secondary Analyses

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm will also be evaluated. The 95% CIs will be constructed in the same manner as for the primary efficacy endpoint. However, non-inferiority will be assessed using a margin of 10%. It will be concluded that GS-9883/F/TAF is non- inferior to ABC/DTG/3TC if the lower bound of the 2-sided 95% CI of the difference between treatment groups (GS-9883/F/TAF – ABC/DTG/3TC) in the response rate is greater than -10%.

The changes from baseline in CD4+ cell count at Weeks 48 will be summarized by treatment using descriptive statistics. The differences in changes from baseline in CD4+ cell count between the 2 treatment groups and the associated 95% CIs will be constructed using ANOVA models, including treatment (GS-9883/F/TAF vs. ABC/DTG/3TC) as a fixed effect in the model.

In addition, missing CD4+ cell count will be imputed using Last Observation Carried Forward (LOCF) method and analyzed similarly.

8.6. Safety Analysis

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

All safety data collected on or after the date that the study drug was first administered up to the date of the last dose of study drug plus 30 days, unless specified otherwise, will be summarized for subjects in the safety analysis set according to the study drug received.

Data for the pretreatment period and the period post the date of last dose of study drug plus 30 days will be included in data listings for all enrolled subjects.

8.6.1. Extent of Exposure

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

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

Dosing information for individual subjects will be listed.

8.6.2. Adverse Events

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

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event with onset date on or after the study drug start date and no later than 30 days after the study drug stop date; or any adverse event leading to study drug discontinuation.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC, HLT [if applicable], and PT) will be provided by treatment. Additional summaries will include summaries for adverse events by grade, Investigator's assessment of relationship to study drug, and effect on study drug dosing.

On an ongoing basis adverse events will be reviewed for events that might meet the definition of Stage 3 Opportunistic Illnesses in HIV are indicative of an AIDS-Defining Diagnoses. The Gilead medical personnel will review the possible Stage 3 events and approve the events that meet the definition. Those events that do meet the Stage 3 Opportunistic Illness definition of an AIDS-Defining Diagnosis will be listed.

A listing of Stage 3 Opportunistic Illnesses in HIV can be found in Appendix 6.

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the grading scheme defined in Grading of laboratory abnormalities attached in Appendix 5.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by treatment. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent. The maximum postbaseline toxicity grade will be summarized by laboratory parameter.

Laboratory abnormalities that occur before the first dose of study drug or after the last dose of study drug plus 30 days will be included in a data listing.

8.6.4. Bone Safety Evaluations

The percentage changes from baseline in hip/spine BMD at Weeks 48 will be summarized by treatment using descriptive statistics. The differences in percentage changes from baseline in hip/spine BMD between 2 treatment groups and the associated 95% confidence intervals will be constructed using ANOVA models, including treatment as a fixed effect in the model.

In addition, missing values for BMD will be imputed using LOCF method and analyzed similarly.

8.6.5. Other Safety Evaluations

Vital signs and safety ECG data will be summarized as appropriate.

8.7. Pharmacokinetic Analysis

For the intensive PK substudy, plasma concentrations of GS-9883 may be summarized by nominal sampling time using descriptive statistics. Pharmacokinetic parameters (C_{max}, T_{max}, C_{tau}, $AUC_{tau,}$ and $T_{½}$, as appropriate) may be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation %, SD, median, Q1, Q3, minimum, and maximum). Plasma concentrations over time will be plotted in semi-logarithmic and linear formats as mean ± standard deviation, and median (Q1, Q3).

For the general PK analyses, the pharmacokinetics of GS-9883 may be evaluated using descriptive statistics or population approaches.

TAF and FTC concentrations may be analyzed and PK parameters summarized as applicable.

8.8. Inflammation, Immune Activation, Platelet and Renal Tubular Function Analysis

For each selected test of inflammation, immune activation, platelet function, and renal tubular function, the percentage changes from baseline will be summarized by treatment and visit using descriptive statistics. Differences in percentage changes from baseline in each selected test between the 2 treatment groups will be tested using a Wilcoxon rank sum test.

8.9. Patient Reported Outcomes (PRO)

The PRO measures based on questionnaires (eg, SF-36 and HIV Symptoms Distress Module) may be summarized by treatment and visit using descriptive statistics.

8.10. Sample Size

A total of approximately 520 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 treatment groups (260 subjects per treatment group), achieves at least 90% power to detect a non-inferiority margin of 4% difference in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 between the 2 treatment groups. For the sample size and power computation, it is assumed that both treatment groups have 2% of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 (based on the historical Gilead E/C/F/TAF and STB studies), that the non-inferiority margin is 4%, and that the significance level of the test is at a one-sided 0.025 level. Sample size and power calculations were made using the statistical software package nQuery Advisor (Version 6.0).

8.11. Data Monitoring Committee

An external Independent Data Monitoring Committee (IDMC) will review the progress, efficacy, and safety data of this study while the study is ongoing. The committee will convene after approximately the first 50% of subjects enrolled have completed their Week 12 Visit or prematurely discontinued from the study drug, as well as after all subjects have completed their Week 24 Visit or prematurely discontinued from the study drug. However, Gilead will defer to the IDMC for any decision to convene earlier or more frequently. The IDMC will examine the safety results of the trial and also focus on logistical issues such as accrual, retention, quality of clinical and laboratory data, and implications of results of external studies. Blinding will be preserved during the conduct of the study and access to unblinded data will be limited to designated parties.

No formal stopping rules will be used by the IDMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of adverse events associated with a study regimen warrant the early termination of the study in the best interest of the participants.

For each IDMC analysis performed prior to the analysis of the primary efficacy endpoint, an alpha penalty of 0.00001 will be applied for the primary analysis of the primary endpoint.

8.12. Analysis Schedule

The Week 48 analysis will be conducted after all subjects either complete their Week 48 visit or prematurely discontinue from the study drug, respectively. Final analysis will be performed after all subjects complete the study or prematurely discontinue from the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

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

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

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

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The

investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (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, 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 IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

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

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

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. 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. Investigational Medicinal Product Accountability and Return

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

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

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(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

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Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed

GS-US-380-1844 Amendment 2, 19 October 2016

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

Hal Martin
Hal Martin, MD, MPH (Printed)

PPD
Signature

20 Oct 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 (Blinded Phase)

Study Procedures	Screening[a]	Day 1[b]	End of Week[e, p]						Post-Week 48[e, q]	End of Blinded Treatment Visit	30-Day Follow-up[o]	Early Study Drugs DC[c]
			4	8	12	24	36	48	Every 12 Weeks			
Informed Consent	X											
Medical History	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Complete/Symptom-Directed Physical Exam	**X**	**X**	X[d]	X[d]	X[d]	**X**	X[d]	**X**	X[d]	**X**	X[d,f]	**X**[f]
12-Lead ECG (performed supine)	X	X				X		X		X		X
Questionnaires		X	X		X			X				
DXA scan (spine & hip)[g]		X				X		X		X		X
Height	X											
Vital signs (blood pressure, pulse, respiration rate, and temperature), including Weight	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Urine Pregnancy Test[h]		X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test	X											
Chemistry Profile[i]	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Metabolic Assessments[j]		X			X	X		X	X[r]	X		
Estimated Glomerular Filtration Rate	X	X	X	X	X	X	X	X	X	X	X[f]	X
Hematology Profile[k]	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedures	Screening[a]	Day 1[b]	End of Week[e, p]						Post-Week 48[e, q]	End of Blinded Treatment Visit	30-Day Follow-up[o]	Early Study Drugs DC[c]
			4	8	12	24	36	48	Every 12 Weeks			
Evaluations of inflammation and immune activation, platelet function and renal tubular function		X				X		X	X[r]	X		
Plasma & Urine Storage Sample		X	X	X	X	X	X	X	X	X		X
Whole Blood sample for potential HIV DNA genotyping		X										
HBV and HCV Serology	X							X	X[u]			
HIV-1 Genotype/Phenotype[e]												X[e]
Single PK Sample[l]				X		X	X					
Trough PK Samples[m]			X		X							
Optional Whole blood/EDTA for HLA testing, UGT1A1 and biomarkers		X										
Randomization[t]		X										
Provide subject dosing diary to subjects		X	X	X	X	X						
Optional PK Substudy[n]			X	X								
Study Drug Dispensation		X[b]	X	X	X	X	X	X	X	X[s]		
Study Drug Accountability			X	X	X	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Day 1.
b Initiation of the first dose of study drug is to take place in-clinic following completion of study procedures at the Day 1 visit, with the exception of DXA.
c Early Study Drugs Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Visit even if the subject discontinues study drug.
d Symptom-directed physical examination as needed.
e HIV-1 genotype and phenotype testing for subjects with virologic failure. Following virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease, and integrase genotype and phenotype) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Sections 6.13.1 and 6.13.2).
f Any adverse event or test showing abnormal results that is believed to have 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.

g DXA scans to be performed in all eligible subjects on study drug, except for those in Germany, prior to or within 24 hours of the Day 1 Visit, Weeks 24, 48 (±10 days), at End of Blinded Treatment Visit (±10 days) and the ESDD visit (if the last scan was acquired > 12 weeks from the date of the End of Blinded Treatment Visit or ESDD Visit).

h Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.

i Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) At Day 1, Weeks 12, 24, 48 and End of Blinded Treatment Visit, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. Additionally: TSH will be analyzed at Screening, Day 1, Weeks 24 and 48 followed by every 24 weeks post Week 48, End of Blinded Treatment Visit, and Early Study Drugs Discontinuation visit.

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

k CBC with differential and platelet count.

l A single PK blood sample will be collected at any time pre or post-dose

m A trough PK blood sample will be collected between 20-28 hours following the last dose. Following an observed dose, a single post dose blood sample will be collected between 1 and 4 hours post dose.

n A PK substudy will be performed in a subset of subjects (n=30) at selected study sites. The pharmacokinetic substudy visit must occur at the **Week 4 or Week 8** visits. The substudy will include intensive PK profiling in plasma

o Only required for those subjects not enrolling in the Open-Label Rollover Extension, those subjects who prematurely discontinue study drugs and do not continue in the study through at least one subsequent visit after the Early Study Drugs Discontinuation Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.

p Study visits are to be completed within ± 2 days of the protocol-specified visit date based on the Day 1 visit through Week 12 and completed within ± 6 days through to Week 36, unless otherwise specified. The visit window at Weeks 48 will be ± 6 weeks of the protocol-specified visit date.

q After Week 48, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit. Visit window of ± 6 days for study visits post Week 48.

r To be performed every 24 weeks after Week 48 until End of Blinded Treatment Visit.

s Open label study drug, GS-9883/F/TAF FDC will be dispensed to subjects participating in the Open-Label Rollover Extension for up to 96 weeks.

t Randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed.

u To be performed every 48 weeks.

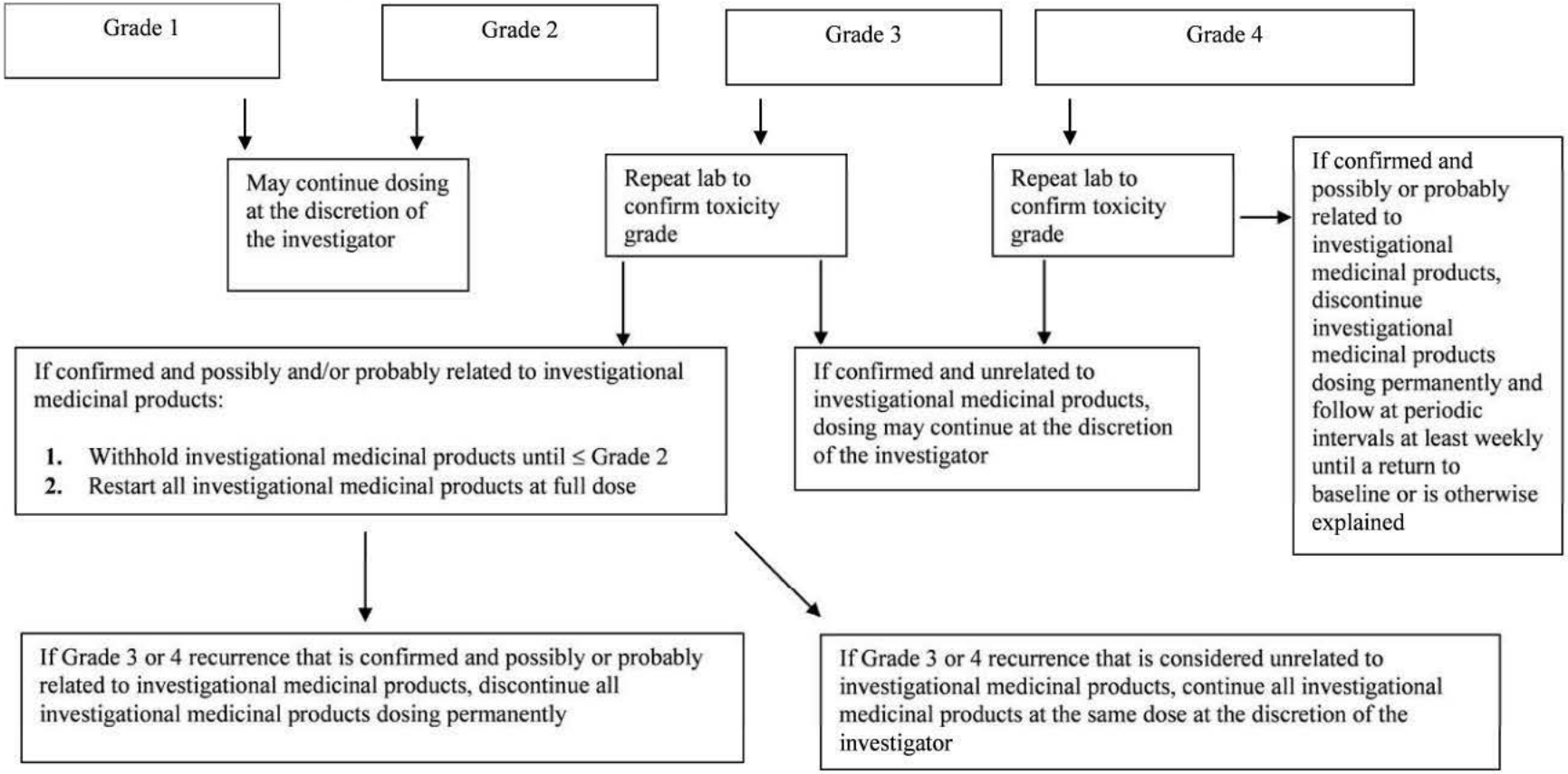
Appendix 3. Study Procedures Table (Open-Label Rollover Extension)

Study Procedures	End of Blinded Treatment Visit[a]	End of Week[e, l]								30-Day Follow-up[k]	Early Study Drugs DC[c]
		12 OL	24 OL	36 OL	48 OL	60 OL	72 OL	84 OL	96 OL		
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[f]	X[f]
Complete/Symptom-Directed Physical Exam	X	X[d]	X[d]	X[d]	X	X[d]	X[d]	X[d]	X	X[d,f]	X[f]
12-Lead ECG (performed supine)	X				X				X		
DXA scan (spine & hip)[m]	X										
Vital signs (blood pressure, pulse, respiration rate, and temperature), including Weight	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Urine Pregnancy Test[g]	X	X	X	X	X	X	X	X	X	X	X
Chemistry Profile[h]	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Metabolic Assessments[i]	X		X		X		X		X		
Estimated Glomerular Filtration Rate	X	X	X	X	X	X	X	X	X	X[f]	X
Hematology Profile[j]	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X
Evaluations of inflammation and immune activation, platelet function and renal tubular function	X										
Plasma & Urine Storage Sample	X	X	X	X	X	X	X	X	X		X
HBV and HCV Serology					X				X		
HIV-1 Genotype/Phenotype[e]											X[e]

Study Procedures	End of Blinded Treatment Visit[a]	End of Week[e, l]								30-Day Follow-up[k]	Early Study Drugs DC[c]
		12 OL	24 OL	36 OL	48 OL	60 OL	72 OL	84 OL	96 OL		
Study Drug Dispensation[b]	X	X	X	X	X	X	X	X			
Study Drug Accountability	X	X	X	X	X	X	X	X	X		X

a. Once the last subject completes the Week 48 visit and Gilead completes the Week 48 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of GS-9883/F/TAF is demonstrated following review of unblinded data, subjects in a country where GS-9883/F/TAF FDC is not available, will be given the option to receive GS-9883/F/TAF FDC in an open-label extension phase for up to 96 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first. Treatment assignments will be provided to the investigators within 30 days of the last subject completing the End of Blinded Treatment Visit.
b. Open-label study drug, GS-9883/F/TAF FDC will be dispensed to subjects participating in the Open-Label Rollover Extension for up to 96 weeks.
c. Subjects who discontinue study drug during the open-label rollover extension portion of the study will be asked to return to the clinic within 72 hours of stopping study drugs for the Early Study Drugs Discontinuation Visit followed by a 30-Day Follow-Up Visit. The subject will not continue attending the scheduled study visits.
d. Symptom-directed physical examination as needed.
e. HIV-1 genotype and phenotype testing for subjects with virologic failure. Following virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease, and integrase genotype and phenotype) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Sections 6.13.1 and 6.13.2).
f. Any adverse event or test showing abnormal results that is believed to have 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.
g. Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
h. Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). At the End of Blinded Treatment Visit, Week 24 OL and Week 48 OL, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. For all subjects, TSH will be done at the End of Blinded Treatment Visit, Week 24 OL, Week 48 OL, Week 72 OL, Week 96 OL and Early Study Drug Discontinuation Visit.
i. Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
j. CBC with differential and platelet count.
k. Subjects who complete the Open-Label Rollover Extension 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 drugs during the Open-Label Rollover Extension will be asked to return to the clinic 30 days after the completion of the Early Study Drugs Discontinuation Visit for the 30-Day Follow-Up Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.
l. Study visits are to be completed within ± 6 days of the protocol-specified visit date based on the End of Blinded Treatment Visit date, unless otherwise specified.
m. DXA scans to be performed in all eligible subjects on study drug, except for those in Germany, at the End of Blinded Treatment Visit (±10 days) if the last scan was acquired > 12 weeks from the date of the End of Blinded Treatment Visit.

Appendix 4. Management of Clinical and Laboratory Adverse Events



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

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Infant <1 Year	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 mmolL	2.0 to < 2.5 mEq/L 2.0 to <2.5 mmolL	< 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	>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	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **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

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

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

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

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

Notes:

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

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

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

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

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

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

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

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)

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

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

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

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

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

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

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

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

Appendix 6. Definitions of Stage 3 Opportunistic Illnesses in HIV (CDC Guidelines)

1. Candidiasis of bronchi, trachea, or lungs
2. Candidiasis of esophagus
3. Cervical cancer, invasive
4. Coccidioidomycosis, disseminated or extrapulmonary
5. Cryptococcosis, extrapulmonary
6. Cryptosporidiosis, chronic intestinal (> 1 month duration)
7. Cytomegalovirus disease (other than liver, spleen or nodes)
8. Cytomegalovirus retinitis (with loss of vision)
9. Encephalopathy, HIV-related
10. Herpes simplex: chronic ulcer(s) (> 1 month duration); or bronchitis, pneumonitis or esophagitis
11. Histoplasmosis, disseminated or extrapulmonary
12. Isosporiasis, chronic intestinal (> 1 month duration)
13. Kaposi's sarcoma
14. Lymphoma, Burkitt's (or equivalent term)
15. Lymphoma, immunoblastic (or equivalent term)
16. Lymphoma, primary, of brain
17. *Mycobacterium avium* complex or *Myobacterium kansasii*, disseminated or extrapulmonary
18. *Mycobacterium tuberculosis*, of any site, pulmonary, disseminated or extrapulmonary
19. *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
20. Pneumocystis jirovecii (previously known as "*Pneumocystis carinii*) pneumonia
21. Pneumonia, recurrent
22. Progressive multifocal leukoencephalopathy
23. *Salmonella* septicemia, recurrent
24. Toxoplasmosis of brain
25. Wasting syndrome attributed to HIV infection

CDC Stage-3-Defining Opportunistic Illnesses in HIV Infection - 2014 {Schneider et al 2008}

Appendix 7. 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 to be 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 on GS-9883/F/TAF in 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 studies for human pregnancy do not indicate a strong suspicion of human teratogenicity/fetotoxicity. Data from clinical pharmacokinetic interaction studies of GS-9883 and F/TAF 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 GS-9883/F/TAF investigator's brochure and the current Prescribing Information and local product labeling for ABC/DTG/3TC 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 have a negative serum pregnancy test at Screening and a negative pregnancy test on the Day 1 visit prior to randomization. At minimum a pregnancy test will be performed at the end of relevant systemic exposure. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even 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
  - Intrauterine hormone-releasing system (IUS) 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
    - 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

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days after the end of relevant systemic exposure. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after the end of relevant systemic exposure.

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. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.3.