CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Open Label Study to Evaluate the Safety and Efficacy of Switching to a Fixed Dose Combination (FDC) of GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) from Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (E/C/F/TAF), Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate (E/C/F/TDF) or Atazanavir + Ritonavir + Emtricitabine/Tenofovir Disoproxil Fumarate (ATV+RTV+FTC/TDF) in Virologically Suppressed HIV-1 Infected Women	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	125589	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	NCT02652624	
Indication:	HIV-1 Infection	
Protocol ID:	GS-US-380-1961	
Gilead Clinical Program Manager:	Name: Telephone: Fax:	PPD PPD PPD
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Protocol Version/Date:	Original: Amendment 1:	20 November 2015 30 June 2016

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Study Title:	A Phase 3, Randomized, Open Label Study to Evaluate the Safety and Efficacy of Switching to a Fixed Dose Combination (FDC) of GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) from Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF), Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (E/C/F/TDF) or Atazanavir + Ritonavir + Emtricitabine/Tenofovir Disoproxil Fumarate (ATV+RTV+FTC/TDF) in Virologically Suppressed HIV-1 Infected Women
IND Number:	125589
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT02652624
Study Centers Planned:	Approximately 75 centers in North America, Dominican Republic, Thailand, Russia, and Uganda
Objectives:	The primary objective of this study is: • To evaluate the efficacy of switching to an FDC of GS-9883/F/TAF versus continuing on a regimen consisting of E/C/F/TAF, E/C/F/TDF or ATV+RTV+FTC/TDF in virologically suppressed HIV-1 infected women as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 The secondary objective of this study is: • To evaluate the safety and tolerability of the treatment groups through Week 48
Study Design:	Randomized, open label, multicenter, active-controlled study to evaluate the safety and efficacy of switching to an FDC of GS-9883/F/TAF in HIV-1 infected women who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF for ≥ 12 consecutive weeks prior to screening.

	Subjects will be HIV-1 infected women drawn from prior participation in Gilead clinical studies with ARV regimens consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF and must be virologically suppressed. Women who are currently suppressed on a commercially based ARV regimen, either Stribild® (STB) or Genvoya®, may also be eligible. Subjects who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to receive open label medication as follows: • **Treatment Group 1:** 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 = 200) • **Treatment Group 2:** Stay on baseline regimen (SBR), including E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF administered orally, once daily, with food (n = 200) Randomization will be stratified by the prior treatment regimen group (ie, E/C/F/TAF, E/C/F/TDF, and ATV+RTV+FTC/TDF).
Number of Subjects Planned:	Approximately 400 subjects total Approximately 200 subjects in each Treatment Group 1 and Treatment Group 2
Target Population:	HIV-1 infected women who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF for ≥ 12 weeks prior to screening
Duration of Treatment:	Subjects will be treated for at least 48 weeks. At the Week 48 Visit, 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 for an additional 48 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 complete the study through the Week 48 Visit and do not continue participation in the study will be required to return to the clinic 30 days after the Week 48 Visit for a 30 Day Follow-Up Visit.

Diagnosis and Main Eligibility Criteria:	Medically stable HIV-1 infected women who meet the following criteria: • Currently on a stable antiretroviral regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF continuously for ≥ 12 consecutive weeks preceding the screening visit • Documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 12 weeks preceding the Screening visit. After reaching HIV-1 RNA < 50 copies/mL, single values of HIV-1 RNA ≥ 50 copies/mL followed by re-suppression to < 50 copies/mL is allowed • HIV-1 RNA <50 copies/mL at screening • Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault (C-G) formula 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 Screening and Day 1 visits, subjects will return for study visits at Weeks 4, 8, 12, and then every 12 weeks until the Week 48 visit. For all eligible subjects, blood and urine will be collected at Day 1, Weeks 4, 8, 12, and then every 12 weeks through the Week 48 visit. Laboratory analyses (including 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. 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:	Current antiretroviral drug regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF administered orally, once daily, with food.
Criteria for Evaluation:	
Safety:	Adverse events and clinical laboratory tests to evaluate the safety and tolerability of the treatment regimens.

Efficacy:	The primary efficacy endpoint is: • The proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm. The secondary efficacy endpoints include: • The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm • The change from baseline in CD4+ cell count at Week 48
Pharmacokinetics:	For all subjects on GS-9883/F/TAF (Treatment Group 1), a single anytime pre or post-dose PK blood sample will be collected at Weeks 8, 24, and 36. For all subjects on GS-9883/F/TAF (Treatment Group 1), 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 PK blood sample will be collected between 1 and 4 hours post-dose. Additionally, in a subset of subjects at selected sites who become pregnant, matching maternal and umbilical cord blood will be obtained at delivery to assess placental transfer of study drug. The concentration of GS-9883 may be summarized using descriptive statistics.
Statistical Methods:	The primary analysis will consist of a non-inferiority test of switching to GS-9883/F/TAF FDC versus SBR with respect to the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm. It will be concluded that GS-9883/F/TAF is non-inferior to SBR if the upper bound of the 2-sided 95% confidence interval (CI) of the difference between treatment groups (GS-9883/F/TAF – SBR) in the proportion 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 determined 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 Week 48 will be summarized by treatment using descriptive statistics. The differences and the associated 95% CIs will be constructed using Analysis of Variance (ANOVA) model, including treatment (GS-9883/F/TAF vs. SBR) as a fixed effect in the model.

Adverse events and clinical laboratory assessments will be summarized using descriptive statistics.

A total of approximately 400 HIV-1 infected women, randomized in a 1:1 ratio to 2 treatment groups (200 subjects per treatment group), achieves at least 80% 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 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 Genvoya® and Stribild® (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/DTG/3TC	abacavir/dolutegravir/lamivudine, Triumeq®
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir, Reyataz®
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, C, /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®
EC_{50}	50% effective inhibitory concentration
ECG	electrocardiogram
eCRF	electronic case report form(s)
EVG, E	elvitegravir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, Genvoya®
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

FSH	follicle-stimulating hormone
FTC, F	emtricitabine, Emtriva®
FTC/TAF	emtricitabine/tenofovir alafenamide, Descovy®
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate, Truvada®
GCP	Good Clinical Practice (Guidelines)
GGT	gamma glutamyl transferase
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
IC_{50}	50% maximal inhibitory concentration
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	institutional ethics 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
MT4	human t cell leukemia cell line
nM	nanoMolar
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level

NOEL	no observed effect level
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OCT2	organic cation transporter 2
PI	protease inhibitor
PK	pharmacokinetic
PT	preferred term
PT	prothrombin time
QD	once daily
RAL	raltegravir
RNA	ribonucleic acid
RTV	ritonavir, Norvir®
SAE	serious adverse event
STB	Stribild®, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	tenofovir alafenamide, GS-7340
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

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 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 2013}.

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 NRTI's, 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 half maximal inhibitory concentration (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 the human T cell leukemia MT4 cell line 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 organic cation transporter 2 (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).

Study TX-141-2045 assessed the potential adverse effects of maternal GS-9883 exposure from implantation to weaning on the pregnancy, parturition, and lactation of the maternal Sprague Dawley Rats and on the growth, viability, and development of the neonates. No GS-9883-related effects were noted at any dosage level during the study. Therefore, a dosage level of 300 mg/kg/day (the highest dosage level evaluated) was the NOEL for maternal systemic toxicity, F1 neonatal/developmental toxicity, F1 parental systemic toxicity, F1 reproductive toxicity, and F2 neonatal/early postnatal toxicity of GS-9883 when administered orally (gavage) to F0 maternal Crl:CD(SD) rats. The NOEL corresponds to mean Cmax values of 156 µg/mL and 48 µg/mL and mean AUC0-24 values of 100 µg•h/mL and 1120 µg•h/mL for F0 females (LD10) and F1 pups (PND 10), respectively.

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 (CSR available)

- 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 Study Evaluating the Effect of GS-9883 on Renal Function as Assessed by Markers of Glomerular Filtration Rate (CSR available)

- GS-US-311-1790, a Phase 1 Randomized, 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-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)	5 mg (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}, , which is presented as median (Q1, Q3)

Table 1-3 presents the geometric least squares mean (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 1 b 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 the table below.

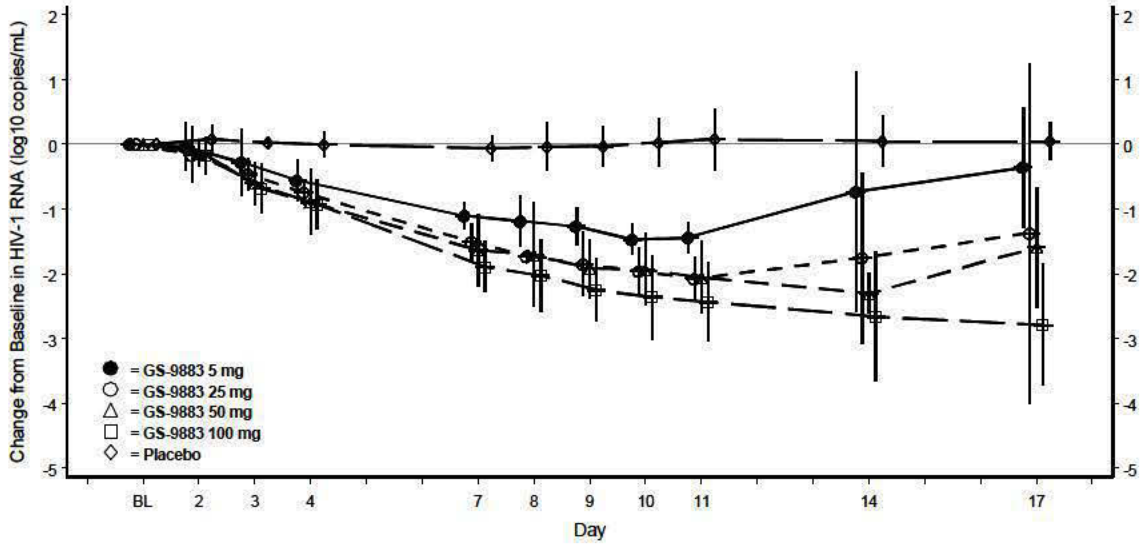
Table 1-4. Trough GS-9883 Plasma Concentrations at Steady State Following GS-9883 Administration Under Fasting Conditions and Corresponding Protein-Adjusted IQ_{95} Values (GS-9883 PK Analysis Set)

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 IQ_{95} ($paIQ_{95}$) 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).

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, antiretroviral therapy (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.

1.2.3.4. 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 study treatment, one 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 estimated glomerular filtration rate [eGFR] using the Cockcroft-Gault method [$eGFR_{CG}$]) were similar between the 2 treatment groups.

Median (Q1, 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.

1.2.3.5. Efficacy Results

Virologic success at Week 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 1 was considered a virologic failure by US FDA-defined snapshot algorithm with HIV-1 RNA of 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 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 at 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.

1.2.3.6. Safety Results

Adverse Events

The overall incidence of treatment-emergent AEs was balanced between treatment groups as follows: GS-9883+F/TAF 58.5%, 38 subjects; DTG+F/TAF 57.6%, 19 subjects. The most common TEAEs (occurring in > 1 subject) 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, and 1 other SAE (appendicitis), also in the GS-9883+F/TAF group, was reported. Neither SAE was considered related to study drug by the investigator, resulted in study drug discontinuation, or required interruption of study drug, 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 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 treatment-emergent laboratory abnormalities occurring in at least 2 subjects in either treatment group were as follows: creatine kinase (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 Food and Drug Administration (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-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 a 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 CSR is available; 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 50 mg 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 in the 50 mg FDC with AUC_{inf} increasing by 24%. The steady state $_{pa}IQ_{95}$ of GS-9883/F/TAF (50/200/25 mg) following multiple doses 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 in the 50 mg FDC 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. EVG/COBI/FTC/TDF (E/C/F/TDF or Stribild®)

Further information is available in the US Prescribing Information and Investigator's Brochure for E/C/F/TDF.

1.7. Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF, Truvada®)

Further information is available in the Prescribing Information for Truvada®.

1.8. Ritonavir (RTV, /r, Norvir®)

Further information is available in the Prescribing Information for Norvir®.

1.9. Atazanavir (ATV, Reyataz®)

Further information is available in the Prescribing Information for Reyataz®.

1.10. 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 an 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. In addition, the benefit/risk balance of administration of GS-9883/F/TAF to pregnant women is considered favorable as demonstrated by the lack of findings in pre and postnatal nonclinical studies. Approximately 50% of the global population of HIV-infected persons are women, however they remain under-represented in most clinical HIV studies. In general, studies to date have not shown gender differences in virologic responses to antiretroviral therapy (ART), but a number of studies have suggested that gender may influence the frequency, presentation, and severity of selected ARV-related adverse events. Although data are limited, the pharmacokinetics for some ARV drugs may differ between men and women, possibly because of variations in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, CYP450 activity, drug transporter function, and excretion activity. It is important to understand potential gender-specific safety and efficacy issues in women when assessing virologic response, tolerability, and adherence. This study will ensure that there is adequate safety data in HIV-1-infected women in the Phase 3 program for GS-9883/F/TAF.

The objective of this study is to evaluate the safety and efficacy of an FDC containing GS-9883/F/TAF versus continuing on a regimen consisting of E/C/F/TAF, E/C/F/TDF or ATV+RTV+FTC/TDF in women who are virologically suppressed. Switching to GS-9883/F/TAF offers the advantages of a single-tablet FDC containing the unboosted, next-generation INSTI, GS-9883, combined with a TAF-based nucleotide backbone. GS-9883/F/TAF FDC which includes TAF, has the potential to offer an effective and safer alternative to standard nucleos(t)ide based regimens, without the need for close monitoring of renal or bone toxicities or increase risk of cardiovascular complications as patients age and confront non HIV-related comorbidities.

1.11. Risk/Benefit Assessment for the Study

All patients with HIV-1 infection should receive effective anti-retroviral 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: allergy to any components of the tablets. Protease inhibitors may be associated with increased lipid levels and gastrointestinal side effects. If patients are currently infected with hepatitis B and discontinue their existing or new therapy, there is a risk of severe acute exacerbations of hepatitis B.

In a study of GS-9883 in monkeys, administration of 1000 mg/kg/day (high dose) for 39 weeks resulted in histologic findings of bile duct hyperplasia and hepatocyte hypertrophy. No adverse effects were noted at the mid-dose group (200 mg/kg/day), which had exposures of GS-9883

5.1 times higher than the expected human exposure with administration of GS-9883/F/TAF (50/200/25 mg) tablets. No such findings were seen in rats at any dose. However, the risk of liver or biliary abnormalities in humans receiving GS-9883/F/TAF (50/200/25 mg) for chronic use is unknown. 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.

Potential benefits of GS-9883 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.

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

1.12. 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 – 11.7)
50 mg	4	2170.0 (852.0 – 3020.0)	13.4 (5.3 – 18.6)
100 mg	4	4190.0 (3730.0 – 5970.0)	25.9 (23 – 36.9)

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 interim 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.

E/C/F/TAF

EVG/COBI/FTC/TAF (150/150/200/10 mg) is a fixed dose combination, with only one dose combination available; and has been approved by the United States Food and Drug Administration (FDA) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older with no ARV treatment history or to replace the current ARV regimen in those who are virologically suppressed on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance. This FDC contains the equivalent doses of EVG, COBI and FTC in the marketed product, Stribild® (STB).

E/C/F/TDF (STB)

EVG/COBI/FTC/TDF (150/150/200/300 mg) is a fixed dose combination, with only one dose combination available; and is approved for use (Stribild®) in the United States by the Food and Drug Administration (FDA), for the treatment of HIV-1 infection in treatment-naïve adults.

ATV+RTV+FTC/TDF

ATV (300 mg), RTV (100 mg) and FTC/TDF (200/300 mg) represent the current marketed doses of these products.

1.13. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the efficacy of switching to an FDC of GS-9883/F/TAF versus continuing on a regimen consisting of E/C/F/TAF, E/C/F/TDF or ATV+RTV+FTC/TDF in virologically suppressed HIV-1 infected women as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48.

The secondary objective of this study is:

- To evaluate the safety and tolerability of the treatment groups through Week 48.

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

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

The secondary endpoints include:

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

- The change from baseline in CD4+ cell count at Week 48.

3.2. Study Design

This protocol describes a randomized, open label, multicenter, active-controlled study to evaluate the safety and efficacy of switching to a GS-9883/F/TAF FDC in HIV-1 infected women who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF for ≥ 12 consecutive weeks prior to screening.

3.3. Study Treatments

Subjects who meet one of the following criteria will be given the option to participate in this study:

- Completion of a primary or secondary endpoint visit in an ongoing Gilead study with ARV regimens consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF, or

- Currently suppressed on a commercially based, single tablet regimen (STR) consisting of E/C/F/TAF (Genvoya®) or E/C/F/TDF (Stribild®)

Subjects who provide written informed consent and meet all eligibility criteria will be randomized in a 1:1 ratio to receive open label medication:

- **Treatment Group 1:** 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 = 200)

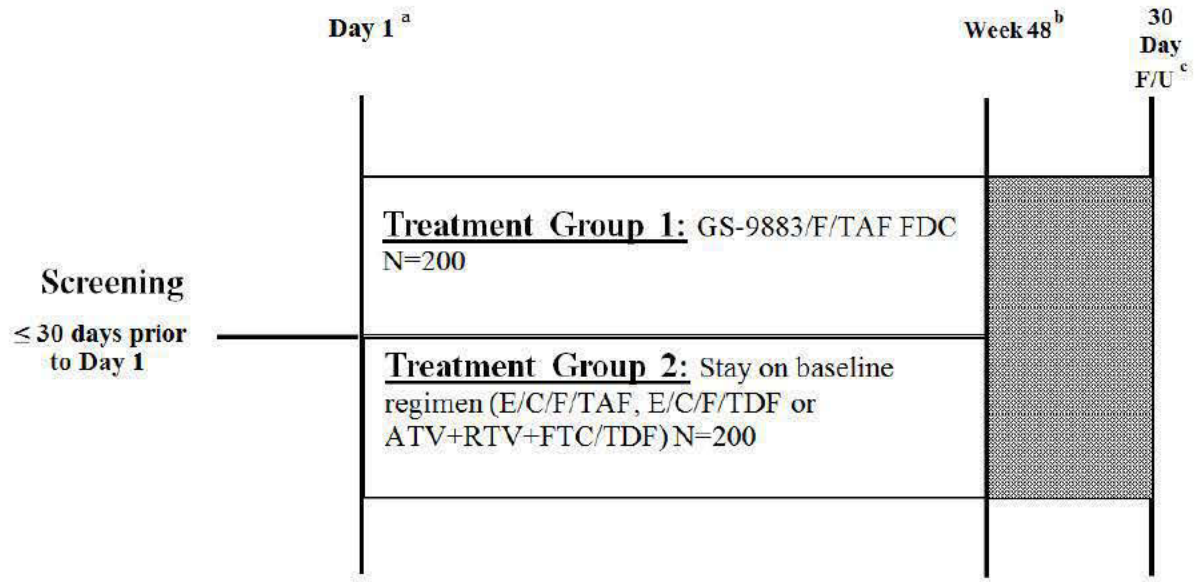
- **Treatment Group 2:** Stay on baseline regimen (SBR), including E/C/F/TAF, E/C/F/TDF or ATV+RTV+FTC/TDF administered orally, once daily, with food (n = 200)

3.4. Duration of Treatment

Subjects will be treated for at least 48 weeks. At the Week 48 Visit, 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 for an additional 48 weeks and attend study visits every 12 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 complete the study through the Week 48 Visit and do not continue post Week 48 will be required to return to the clinic 30 days after the Week 48 Visit for a 30 Day Follow-Up 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 in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF for an additional 48 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

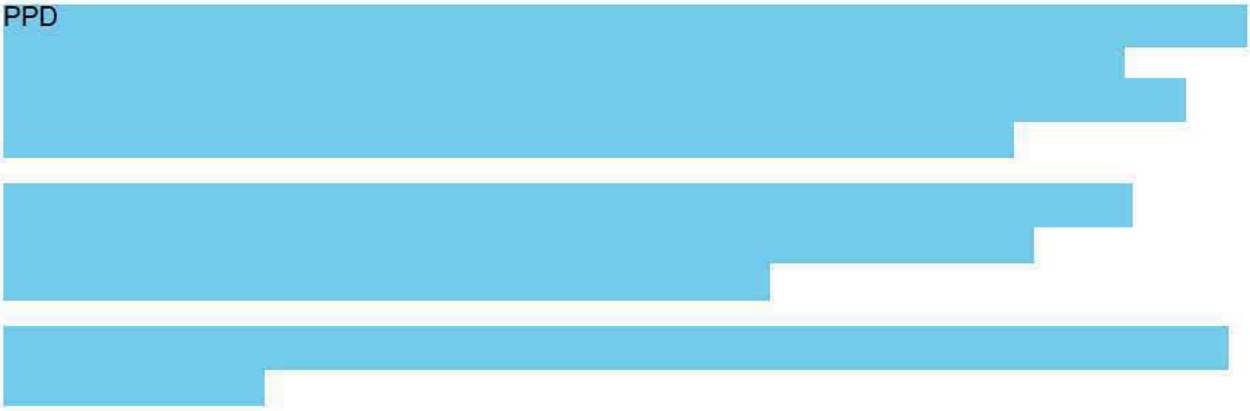
c Subjects who complete the study through Week 48 and do not wish to receive GS-9883/F/TAF FDC will be required to return to the clinic 30 days after the completion of study drug for a 30-day follow-up visit

3.5. Biomarker Testing

3.5.1. Biomarker Samples for Optional Future Research

PPD

PPD



4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 400 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) Female, (at birth), Age ≥ 18 years

3) Currently on a stable antiretroviral regimen of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF continuously for ≥ 12 consecutive weeks preceding the screening visit

4) Completion of the primary or secondary endpoint visit in an ongoing Gilead study, with ARV regimens consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF. Women who are not current Gilead study participants should be on a stable, commercially based ARV drug regimen consisting of E/C/F/TAF or E/C/F/TDF.

5) Documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 12 weeks preceding the Screening Visit. After reaching HIV-1 RNA < 50 copies/mL, single values of HIV-1 RNA ≥ 50 copies/mL followed by resuppression to < 50 copies/mL are allowed

6) HIV-1 RNA < 50 copies/mL at screening

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

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

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

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

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

10) Total bilirubin ≤ 1.5 mg/dL (≤ 26 μmol/L), or normal direct bilirubin.

11) 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)).

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

13) Women 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 6) from screening, throughout the duration of the study period, and for 30 days following the last dose of study drug.

    a) Women 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.

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

14) Have no documented or suspected resistance to FTC, TFV, ATV or EVG 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 5)

2) Subjects experiencing decompensated cirrhosis (eg, 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 (eg, 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 clinical trial other than ongoing Gilead studies with ARV regimens consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF, 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, E/C/F/TAF, E/C/F/TDF, ATV, RTV, or FTC/TDF

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

11) Women who are breastfeeding

12) Subjects receiving ongoing therapy with any of the medications in Table 5-1 or Table 5-2. Administration of any disallowed agent 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) Active tuberculosis infection

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization

Subjects will be assigned a screening number at the time of consent. **Randomization and Day 1 visit 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.

- **Treatment Group 1:** 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 = 200)

- **Treatment Group 2:** Stay on baseline regimen (SBR), including E/C/F/TAF, E/C/F/TDF or ATV+RTV+FTC/TDF administered orally, once daily, with food (n = 200)

The IWRS will assign study drug bottle numbers of open label FDC of GS-9883/F/TAF, open label E/C/F/TAF, open label E/C/F/TDF or open label ATV+RTV+FTC/TDF at each study visit for each subject.

Randomization will be stratified by the prior treatment regimen group (ie, E/C/F/TAF, E/C/F/TDF and ATV+RTV+FTC/TDF).

5.2. Description and Handling

5.2.1. Formulation

5.2.1.1. GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) 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.

5.2.1.2. Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Tablets

E/C/F/TAF tablets are capsule-shaped, film-coated green tablets and are debossed with "GSI" on one side of the tablet and "510" on the other side of the tablet. E/C/F/TAF tablets contain 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide. In addition to the active ingredients, the E/C/F/TAF tablets contain colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet cores are film-coated with indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

5.2.1.3. Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (E/C/F/TDF, Stribild®) Tablets

E/C/F/TDF tablets are capsule-shaped, film-coated green tablets and are debossed with either "GSI" on one side and the number "1" surrounded by a square box on the other side, or "GILEAD" on one side and plain-faced on the other side of the tablet. E/C/F/TDF tablets contain 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate. In addition to the active ingredients, the E/C/F/TDF tablets contain colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet cores are film-coated with indigo carmine (FD&C Blue #2) aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

5.2.1.4. Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF, Truvada®) Tablets

FTC/TDF tablets are capsule shaped film-coated blue and are debossed with "GILEAD" on one side of the tablet and the number "701" on the other side. FTC/TDF tablets contain 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. Further information is available in the Prescribing Information for Truvada®.

5.2.1.5. Ritonavir (RTV, Norvir®) Tablets

RTV tablets, 100 mg, are ovaloid shaped film coated white and are debossed with "aNK" on one side and plain faced on the other side. Further information is available in the Prescribing Information for Norvir®.

5.2.1.6. Atazanavir (ATV, Reyataz®) Capsules

ATV capsules, 300 mg, have a red and blue body and have "BMS 300 mg" in white characters on the cap of the capsule and "3622" in white characters on the body of the capsule. Further information is available in the Prescribing Information for Reyataz®.

5.2.2. Packaging and Labeling

5.2.2.1. GS-9883 50 mg/Emtricitabine 200 mg/Tenofovir Alafenamide 25 mg (GS-9883/F/TAF) Tablets

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.

5.2.2.2. Elvitegravir 150 mg/Cobicistat 150 mg/Emtricitabine 200 mg/ Tenofovir Alafenamide 10 mg (E/C/F/TAF) Tablets

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

5.2.2.3. Elvitegravir 150 mg/Cobicistat 150 mg/Emtricitabine 200 mg/ Tenofovir Disoproxil Fumarate 300 mg (E/C/F/TDF, Stribild®) Tablets

E/C/F/TDF tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and a silica gel desiccant with or without polyester coil fiber. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

5.2.2.4. Emtricitabine 200 mg/Tenofovir Disoproxil Fumarate 300 mg (FTC/TDF, Truvada®) Tablets

Refer to commercially available Prescribing Information.

5.2.2.5. Ritonavir (RTV, Norvir®) Tablets

Refer to commercially available Prescribing Information.

5.2.2.6. Atazanavir (ATV, Reyataz®) Capsules

Refer to commercially available Prescribing Information.

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

5.2.3. Storage and Handling

Study drugs GS-9883/F/TAF FDC, E/C/F/TAF and E/C/F/TDF 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.

Commercial product of Norvir® (RTV), Reyataz® (ATV), and Truvada® (FTC/TDF) will be used for the study. Further information regarding storage and handling are available in the Prescribing Information for commercial products.

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/F/TAF, E/C/F/TAF, E/C/F/TDF and ATV+RTV+FTC/TDF

Study drugs GS-9883/F/TAF FDC, E/C/F/TAF, E/C/F/TDF, and ATV+RTV+FTC/TDF 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) administered orally, once daily, without regard to food (n = 200)

- **Treatment Group 2:** Stay on baseline regimen (SBR), including E/C/F/TAF, E/C/F/TDF or ATV+RTV+FTC/TDF administered orally, once daily, with food (n = 200)

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 tables 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 (GS-9883/F/TAF Regimen)

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 2 hours before and 6 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, Echinaccea	
Oral Hypoglycemic Agent		Metformin: close monitoring is recommended. A dose adjustment of Metformin may be necessary. Limit total daily doses of Metformin to 1000mg either when starting or at study entry.

* 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.

Table 5-2. Prior and Concomitant Medications (E/C/F/TAF, E/C/F/TDF, and ATV+RTV+FTC/TDF Regimens)

Drug Class	Agents Disallowed*
Alpha-1 Adrenoreceptor Antagonist	Alfuzosin
Antiarrhythmic Agent	Amiodarone, Dronedarone
Anticonvulsants	Phenytoin, Carbamazepine and Phenytoin
Antimycobacterials	Rifampin
Antipsychotics	Lurasidone, Pimozide
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen
GI Motility Agents	Cisapride
Herbal/Natural Supplements	St. John's Wort
Anticancer drugs	Irinotecan[a]
Ergot Derivatives	Ergotamine, Ergonovine, Dihydroergotamine, Methylergonovine, Ergometrine
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin
Phosphodiesterase-5 Inhibitors	Sildenafil (for PAH)
Sedatives/Hypnotics	Midazolam (PO), Triazolam
Calcium Channel Blockers	Bepridil
Chronic angina	Ranolazine

a Applied to ATV regimen only
* 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 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 the study prior to enrollment. Please refer to Section 6.3 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 screening visit may coincide with a primary or secondary endpoint visit for subjects in an ongoing Gilead study with ARV regimens consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history including history of HIV-1 disease-related events and prior medications within 30 days of the screening visit
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- 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 (women of childbearing potential only). If the test is positive, the subject will not be enrolled
  - FSH test is required for women who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure

— Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, 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:

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

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

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

— CD4+ cell count

— Plasma HIV-1 RNA

— Hepatitis B Virus (HBV) blood panel: Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb)

The following will be conducted by the central laboratory if the following criteria are met:

- If positive HBsAg, reflex testing for plasma HBV DNA, HBeAg (if negative, reflex HBeAb), and quantitative HBsAg
- If positive HBcAb with negative HBsAg and negative HBsAb, reflex testing for plasma HBV DNA (if positive, reflex HBeAg). If HBeAg is performed and found to be negative, reflex HBeAb

— 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 the Day 1 visit. Subjects must continue to take their current study 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 before being administered the study drug:

- 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
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2 microglobulin
  - Urine pregnancy test (women 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, 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
  - Plasma storage samples for safety, virology, or PK testing
  - Whole blood sample for potential virologic resistance testing and/or HIV DNA genotyping
  - Subjects who meet the definition of HBV infection at Screening Visit (positive serum HBsAg or positive HBcAb with quantifiable HBV DNA), will have plasma HBV DNA tested
- PPD

  P
  P
- Provide subject dosing diary to all subjects in Treatment Group 1
- Dispense study drug
- Subjects in treatment group 1 should be instructed to take study drugs without regard to food. Subjects in treatment group 2 should be instructed to take study drug with food. Subjects are required to initiate dosing of study drugs the day of the Day 1 visit. 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 (Weeks 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 at Week 24 and 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
- 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)**
- 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, subjects may opt to remain on study drug and an additional informed consent would be required.
    - PPD [redacted].
  - 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, 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
- Plasma HBV DNA (for subjects who meet the definition of HBV infection)
    - For subjects who meet the definition of HBV infection, the following will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative) and HBeAg (if negative, reflex HBeAb) **(Weeks 12, 24, and 48)**
- HCV RNA for subjects with positive HCVAb at screening. **(Weeks 24 and 48)**
- Plasma storage sample for safety, virology, or PK testing

- Pharmacokinetic Blood Collection for all subjects on GS-9883/F/TAF only (Treatment Group 1). Details of pharmacokinetic blood sampling procedures and sample management will be documented in the study's laboratory manual.
    - **Single Anytime, Trough and Post-Dose PK Samples: (GS-9883/F/TAF – Treatment Group 1 only)**
        - Subjects will have a single anytime pre or post-dose PK blood sample at **Weeks 8, 24, and 36**
        - Observed dosing at the clinic: If possible, subjects will have a trough PK blood sample collected between 20-28 hours following the 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. 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 single trough PK blood sample collection. In the event a subject routinely takes their study drug in the evening, a single anytime 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. A single PK blood sample will be collected between 1 and 4 hours post dose.
        - 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.

- Provide subject dosing diary to all subjects in Treatment Group 1 **(Weeks 4, 8, 12, and 24)**
- Document study drug dispensation and accountability for all study drugs dispensed

- Subjects who meet the criteria for virologic rebound will be managed according to the Management of Virologic Rebound Section 6.14.1.

- HIV-1 genotype/phenotype testing for subjects with virologic failure **(Week 48)**

6.5. Treatment Assessments (Post Week 48)

6.5.1. Post Week 48 Assessments

At the Week 48 Visit, subjects who completed 48 weeks of study drug treatment and are in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC for an additional 48 weeks and attend study visits every 12 weeks or until the product becomes accessible to subject through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

Subjects who continue participation in the study and receive GS-9883/F/TAF will return for study visits every 12 weeks. Study visits are to be completed within ± 6 days of the protocol-specified visit date unless otherwise specified.

Subjects participating in the study post Week 48 will be required to return for study visits according to the schedule presented in Appendix 2 Study Procedures Table and described in the text below:

- Review of AEs and changes in concomitant medications

- Symptom-directed physical examination as needed

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

- 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, subjects may opt to remain on study drug and an additional informed consent would be required.

    ■ PPD [redacted].

  — 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, 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) TSH will 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
  - Plasma HBV DNA (for subjects who meet the definition of HBV infection)
    - For subjects who meet the definition of HBV infection, the following will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative) and HBeAg (if negative, reflex HBeAb) **(Every 24 Weeks)**
  - HCV RNA for subjects with positive HCVAb at screening. **(Every 24 Weeks)**
  - Plasma storage samples for safety, virology, or PK testing
- Subjects who meet the criteria for virologic rebound will be managed according to the Management of Virologic Rebound Section 6.14.1
- Document study drug dispensation and accountability for all study drugs dispensed.

6.6. Post-Treatment Assessments

6.6.1. Early Study Drugs Discontinuation (ESDD) Assessments

If the subject discontinues study drug prior to the Week 48 Visit, the subject will be asked to return to the clinic within 72 hours of stopping study drug for the Early Study Drugs Discontinuation Visit. The subject will be asked to continue attending the scheduled study visits through the Week 48 Visit.

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

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

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- 12-lead ECG performed supine
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine pregnancy test (women 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, 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 samples for safety, virology, or PK testing
  - Plasma HBV DNA (for subjects who meet the definition of HBV infection)
  - HIV-1 genotype/phenotype testing for subjects with virologic failure
- Drug accountability

6.6.2. 30 Day Follow Up

Subjects who complete the study through the Week 48 visit and do not continue participation in the study 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 permanently discontinue study drug and refuse to continue in the study through the Week 48 visit will be asked to return to the clinic 30 days after the completion of the Early Study Drugs Discontinuation Visit for the 30-Day Follow-Up Visit.

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

Subjects who participate post Week 48 will complete a 30-Day Follow-Up Visit 30 days after last dose of study drug.

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 (women 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, 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 may be discontinued in the following instances:

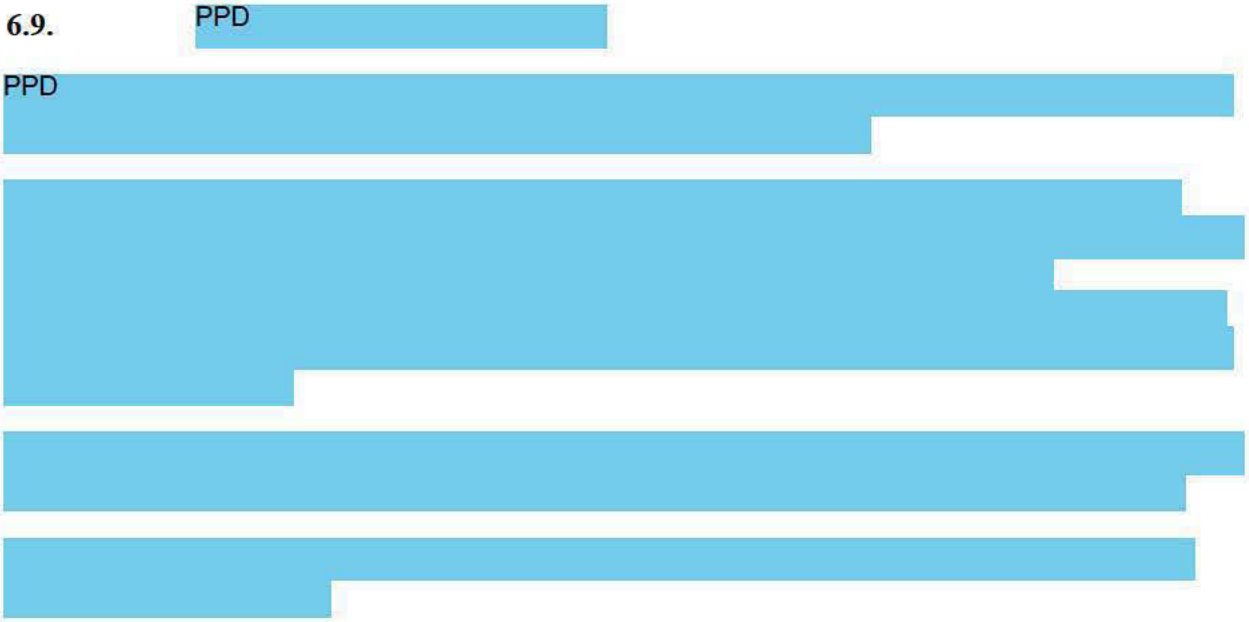
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.
- Unacceptable toxicity, or toxicity that, in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

6.8. Other Evaluations

6.8.1. Markers of Renal Tubular Function

For all subjects, urine will be collected for selected evaluations of renal tubular function, which will include but are not limited to urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2-microglobulin at the Day 1 Visit, Weeks 24, 48, and every 24 weeks post Week 48. At the conclusion of this study, these samples may be retained in storage by Gilead Sciences for a period up to 15 years.

6.9.



6.10. 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 to help answer questions about the study drug, about the disease and its associated conditions and/or 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.

6.11. 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.

6.12. End of Study

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

6.13. 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.

6.14. Virologic Failure

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

6.14.1. 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-Day 1 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.

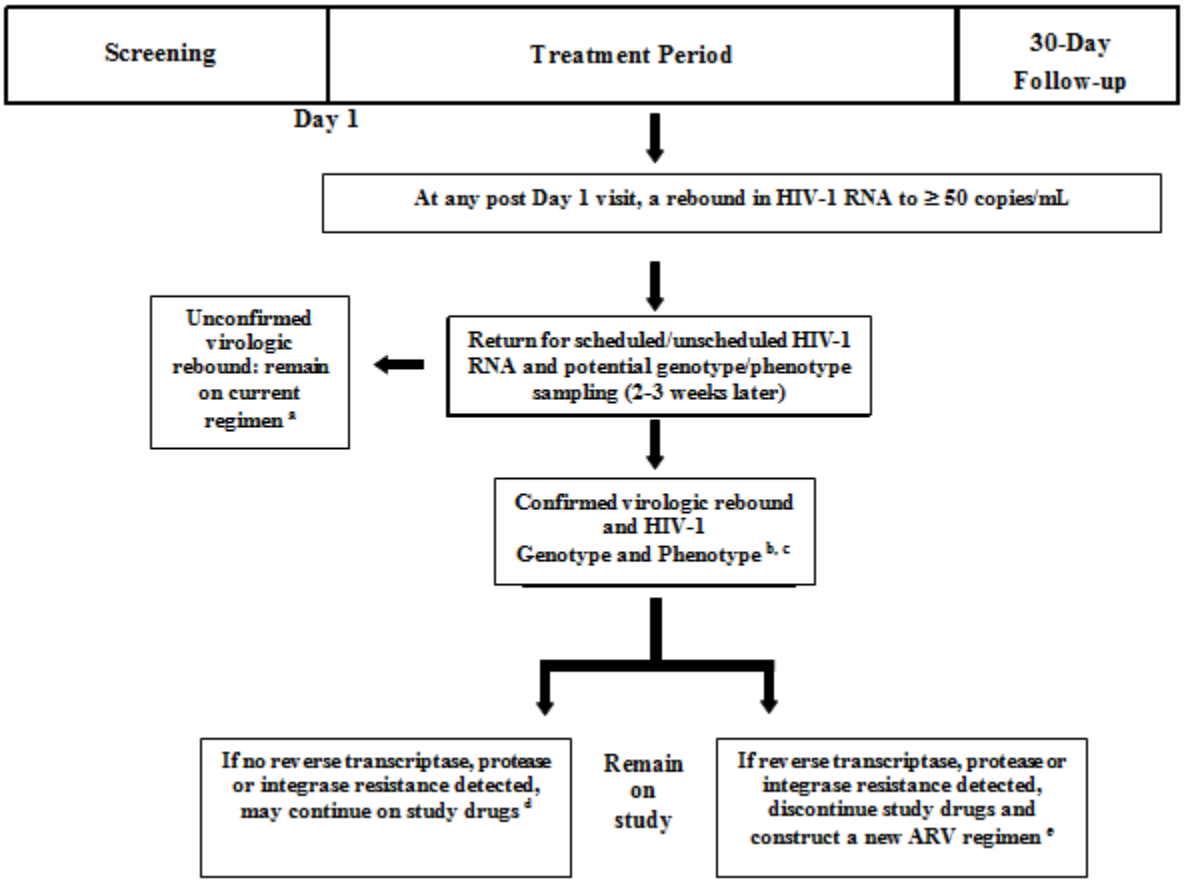
If no resistance is detected from the genotype or phenotype, the subject may remain on study drugs and a repeat HIV-1 RNA should be repeated (2 to 3 weeks after date of test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug for each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

6.14.2. Subjects with HIV-1 RNA ≥ 50 copies/mL at Study 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 4). For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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 case report form (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 (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur 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 Study IMP, he/she should promptly document and report the event to Gilead DSPH.

Electronic Serious Adverse Event (eSAE) Reporting Process

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

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

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

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

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

- 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 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 3 as outlined below.

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

- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before 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 t 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 should 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 should 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 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.

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

An On-Treatment ALT Flare is defined as:

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

7.5.5.1. Management of ALT Flare in Subjects Receiving Study Medication

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

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

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

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

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

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

Elevated Liver Enzymes, Elevated Liver Function Tests

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

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

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

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

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

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

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

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

7.5.6. Management of Hyperbilirubinemia

Most patients taking atazanavir sulfate experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronyl transferase (UGT). Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. Dose modification of atazanavir sulfate is not permitted. Subjects who experience unacceptable jaundice/scleral icterus can be discontinued from study at the discretion of the Investigator.

- Subjects with bilirubin levels of 5-10 × ULN, if isolated and not accompanied by unacceptable clinical jaundice (scleral icterus or cutaneous jaundice) may continue on study, if agreed upon by the subject and the Investigator. All subjects with serum bilirubin levels 5-10 × ULN must have bilirubin, AST and ALT repeated at least once within 7 days of the Investigator being notified of the elevated bilirubin level. Thereafter, serum bilirubin levels 5-10 × ULN without clinically significant elevation in AST or ALT should be followed according to the clinical judgment of the Investigator.

- Subjects whose hyperbilirubinemia (5-10 × ULN) is accompanied by ≥ Grade 2 ALT or AST elevation or who experience a one Grade worsening in ALT or AST do not qualify as having isolated hyperbilirubinemia and will be discontinued.

- Confirmed hyperbilirubinemia > 10 × ULN will require discontinuation.

- Elevation of conjugated (direct) bilirubin > 2 mg/dL in association with Grade 2 ALT or AST elevation will require discontinuation.

7.5.7. 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.

7.5.8. Management of Potential Nephrotoxicity

Estimated glomerular filtration rate according to the Cockcroft-Gault formula ($eGFR_{C-G}$), will be followed post-baseline during the study. All subjects with estimated GFR < 50 mL/min (0.83 mL/sec) must have serum creatinine and subject's weight measured again within 3 calendar days of receipt of results.

If a subject has confirmed $eGFR_{C-G}$ < 50 mL/min, the Medical Monitor should be notified and discontinuation of the study drug should be discussed. For subjects with confirmed $eGFR_{C-G}$ < 50 mL/min who are not discontinued based on toxicity management procedures above and are considered to have stable renal function per Principal Investigator and Medical Monitor, it is not mandatory to repeat eGFR assessments within 3 days.

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

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.

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in 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 or SAE term, as applicable.

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

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

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

Refer to Appendix 6 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 7.6 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 to a GS-9883/F/TAF FDC versus staying on baseline regimen (SBR) in virologically suppressed HIV-1 infected women as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48.

The secondary objective of this study is to evaluate the safety, and tolerability of the two treatment groups 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 determined 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 determined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count 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 (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 (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 5 including drugs not to be used with GS-9883, FTC, TAF, EVG, COBI, ATV, and RTV.
- Non adherence 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) 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 non missing PK concentration data for the analyte under evaluation reported by the PK lab.

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. 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 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 determined by the US FDA-defined snapshot algorithm. The primary analysis of the efficacy 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 reasons 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 is < 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 SBR 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 SBR group.

Non-inferiority will be assessed using the conventional confidence interval (CI) approach. The point estimate of treatment difference (GS-9883/F/TAF – SBR) 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 E/C/F/TAF if the upper bound of the 2-sided 95% CI of the difference between treatment groups (GS-9883/F/TAF – SBR) 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).

If non-inferiority of GS-9883/F/TAF to SBRis 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 SBR will be established.

8.5.2. Secondary Analyses

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined 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 SBRif the lower bound of the 2-sided 95% CI of the difference between treatment groups (GS-9883/F/TAF - SBR) in the response rate is greater than −10%.

The changes from baseline in CD4+ cell count at Week 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. SBR) 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 Illnesses definition of an AIDS-Defining Diagnosis will be listed.

A listing of Stage 3 Opportunistic Illnesses in HIV can be found in Appendix 5.

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 4.

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 (i.e., at least a Grade 1) will be considered treatment emergent. The maximum post baseline 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. Other Safety Evaluations

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

8.7. Pharmacokinetic Analysis

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

TAF and FTC concentrations may be analyzed as applicable.

8.8. Sample Size

A total of approximately 400 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 treatment groups (200 subjects per treatment group), achieves at least 80% power to detect a non-inferiority margin of 4% difference in percentage of subjects with HIV-1 RNA $\geq$ 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 $\geq$ 50 copies/mL at Week 48 (based on the historical Gilead Genvoya® 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.

8.9. Independent 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 all subjects enrolled complete Week 24 of the study or prematurely discontinue 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.

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.

An analysis for the Week 24 IDMC meeting will be conducted after the last subjects enrolled completes Week 24 of the study. For each IDMC analysis performed prior to analysis for the primary efficacy endpoint, an alpha penalty of 0.00001 will be applied for the primary analysis of the primary efficacy endpoint.

8.10. 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. 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, CRF and query forms, IRB/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 casebook will be completed by an authorized study staff member whose training for this function is completed in EDC. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for

responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. 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/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/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

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

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

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Open Label Study to Evaluate the Safety and Efficacy of Switching to a Fixed Dose Combination (FDC) of GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) from Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF), Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (E/C/F/TDF) or Atazanavir + Ritonavir + Emtricitabine/Tenofovir Disoproxil Fumarate (ATV+RTV+FTC/TDF) in Virologically Suppressed HIV-1 Infected Women

GS-US-380-1961, Amendment 1, 30 June 2016

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

HUYEN CAO
Huyen Cao, MD (Printed)
Author

PPD

30 JUN 2016
Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						Post Week 48[d,v]	30 Day Follow-Up[e]	ESDD[f]
			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
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X	X				X		X			X
Symptom-Directed Physical Exam			X	X	X		X		X	X	
12-Lead ECG	X	X				X		X			X
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
Urine Chemistry[h]		X				X		X	X[w]		
Urine Pregnancy Test[i]		X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[i]	X										
Chemistry Profile[j]	X	X	X	X	X	X	X	X	X	X	X
Metabolic Assessments[k]		X			X	X		X	X[w]		
Estimated GFR	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile[l]	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA[m]	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
HBV Blood Planel[n]	X										

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						Post Week 48[d,v]	30 Day Follow-Up[e]	ESDD[f]
			4	8	12	24	36	48	Every 12 Weeks		
Plasma HBV DNA[o]		X			X	X		X	X[w]		X
HCVAb[p]	X										
HCV RNA[p]	X					X		X	X[w]		
HIV-1 Genotype/Phenotype[q]								X[q]			X[q]
Single PK Draw[r]				X		X	X				
Trough PK Draw[s]			X		X						
PK Sample (post-dose)[s]			X		X						
Observed In-Clinic Dose[s]			X		X						
Provide Dosing Diary[u]		X	X	X	X	X					
Collect Dosing Diary[x]			X	X	X	X	X				
Plasma Sample Storage[t]		X	X	X	X	X	X	X	X		X
Urine Sample Storage[t]		X	X	X	X	X	X	X	X		X
Whole Blood Storage Sample[t]		X									
PPD		X									
PPD			X								
Randomization		X									
Study Drug Dispensation		X	X	X	X	X	X	X[v]	X[v]		
Study Drug Accountability			X	X	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Day 1.
b Subjects should initiate dosing of study drug on the same day as the Day 1 visit.
c All study visits should be ± 2 days of the protocol-specified visit date based on the Day 1 visit through Week 12 and completed within ± 6 days at Week 24 and Week 36, unless otherwise specified. The visit window at Week 48 will be ± 6 weeks of the protocol-specified visit date.
d At the Week 48 Visit, 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 for an additional 48 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. Study visits are to be completed every 12 weeks, within ± 6 days of the protocol-specified visit date unless otherwise specified.

e Must be completed 30 days after discontinuing study drug. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used. Required for subjects who permanently discontinue study drug prior to Week 48 and do not continue in the study through at least one subsequent visit after the ESDD visit. Subjects who participate post Week 48 will be required to return to the clinic 30 days after the completion of study drugs for the 30-Day Follow-Up Visit.

f Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the Week 48 Visit even if the subject discontinues study drug.

g Vital signs measurements including blood pressure, pulse, respiratory rate, and temperature

h Urine Chemistry includes urine albumin, urine creatinine, urine protein, retinol binding protein, and beta-2 microglobulin

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

j Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, 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 24, and 48 and every 24 weeks during the post Week 48 period, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. TSH will be collected at Screening, Day 1, Weeks 24, and 48, as well as every 24 weeks post Week 48, and ESDD if applicable.

k Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

l CBC with differential and platelet count.

m If the HIV-1 RNA value is ≥ 50 copies/mL at Week 48, a retest HIV-1 RNA value must be collected within two to three weeks of the initial test.

n Hepatitis B Virus (HBV) blood panel: Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb). If positive HBsAg, reflex testing for plasma HBV DNA, HBeAg (if negative, reflex HBeAb), and quantitative HBsAg. If positive HBcAb with negative HBsAg and negative HBsAb, reflex testing for plasma HBV DNA (if positive, reflex HBeAg). If HBeAg is performed and found to be negative, reflex HBeAb.

o For subjects who meet the definition of HBV infection, the following will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative) and HBeAg (if negative, reflex HBeAb) at Days 1, 12, 24 and then every 24 weeks.

p Subjects who are HCVAb positive will have a HCV RNA test performed at screening and every 24 weeks.

q HIV-1 genotype/phenotype testing for subjects with HIV-1 RNA ≥ 200 copies/mL and virologic rebound, at early study drug discontinuation or Week 48. Following unconfirmed 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/phenotype (reverse transcriptase, protease and integrase) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Section 6.14.1).

r All subjects on GS-9883/F/TAF (Treatment Group 1 only) will have a single anytime PK blood sample collected at Weeks 8, 24 and 36.

s Subjects on GS-9883/F/TAF (Treatment Group 1 only) 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. 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 single trough PK blood sample collection. In the event a subject routinely takes their study drug in the evening, a single anytime 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. A post-dose PK blood sample will be collected between 1 and 4 hours post dose following an observed, in-clinic dose.

t Plasma storage samples banked for possible future protocol-related testing (safety, virology, pharmacokinetic analysis). Urine storage samples banked for possible future protocol-related safety testing including urine chemistry. Whole blood sample for potential virologic resistance testing and/or HIV DNA genotyping. PPD

u A dosing diary will be dispensed for all Treatment Group 1 subjects to complete prior to each of the PK sample visits.

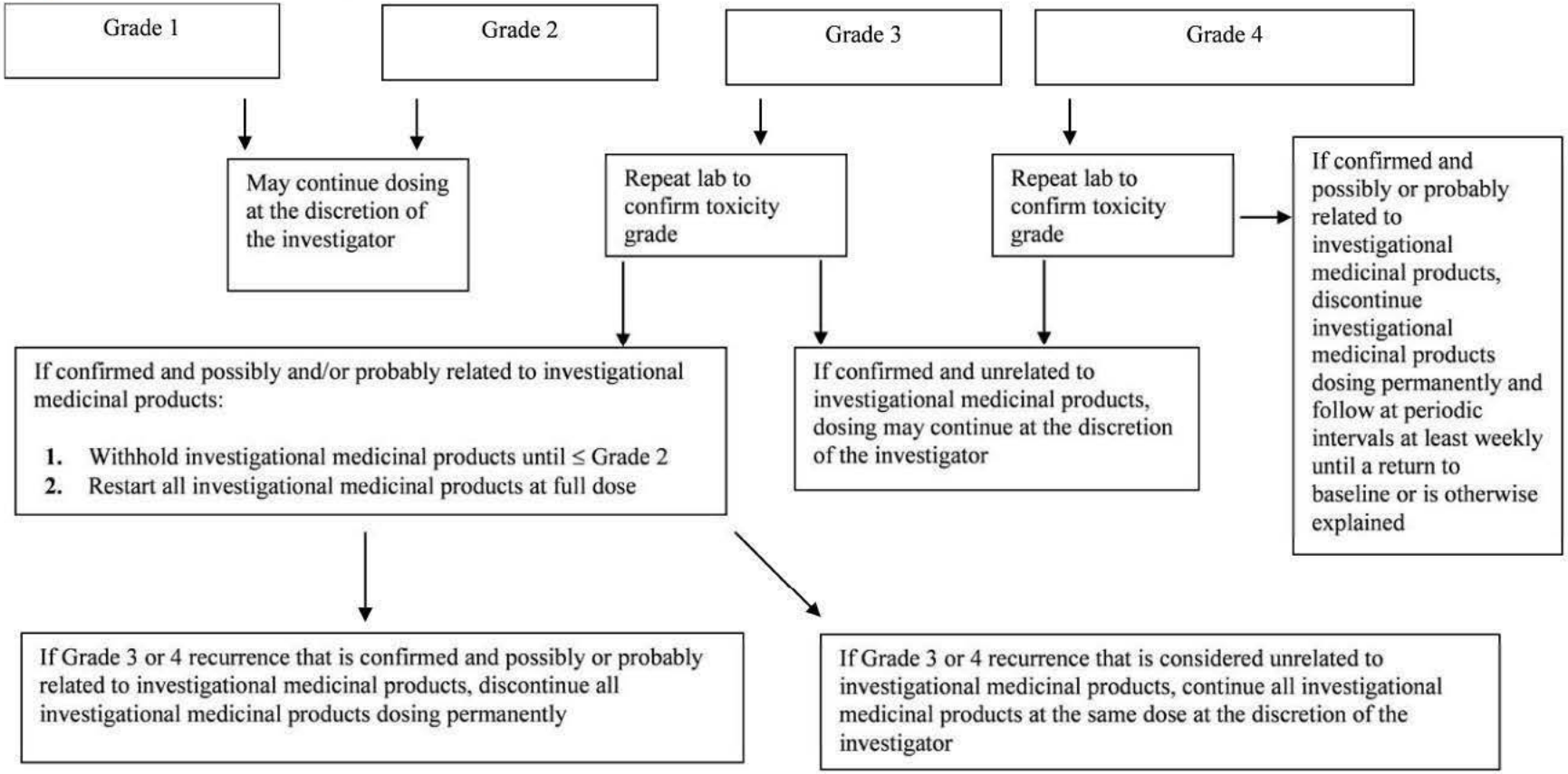
v Open-label GS-9883/F/TAF FDC will be dispensed to subjects participating in the study post Week 48 starting at the Week 48 Visit.

w Every 24 weeks only.

x Dosing diaries will be collected from subjects for the single anytime PK and trough PK collection (Treatment Group 1 only). 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.

y PPD

Appendix 3. Management of Clinical and Laboratory Adverse Events



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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L 3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L 2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L 2.0 to < 2.5 mEq/L 2.0 t o <2.5 mmolL	< 2.0 mEq/L < 2.0 mmol/L < 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L >ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L > 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L > 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L > 7.0 mEq/L > 7.0 mmol/L

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	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

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

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

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

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

Notes:

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

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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
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	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25−81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

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

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

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

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

Appendix 5. 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 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

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

Females are considered to be in a postmenopausal state when they are $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause. In addition, females of any age with amenorrhea of $\geq$ 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.

2) Contraception Requirements for Women

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 latest versions of the E/C/F/TAF, E/C/F/TDF, ATV, RTV and FTC/TDF package inserts or investigator's brochures for additional information.

b. Contraception Requirements for Women 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 a 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) Unacceptable Birth Control Methods

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

4) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 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 immediately. The investigator will counsel the subject regarding pregnancy management options. Counseling will be provided regarding alternative anti-HIV treatment. Information on the risks and benefits of antiretroviral therapies will be discussed, including the risk of ongoing fetal exposure to the study drug versus the new alternative therapy and the risk of discontinuing maternal therapy.

If a subject becomes pregnant during the study, she may opt to remain on study drug and an additional informed consent would be required. PPD [redacted].

If the subject elects to discontinue study drugs but remain in the study, a new ARV regimen will be constructed at the Investigator's discretion.

The Investigator should counsel the subject on the need to inform the study site of the outcome of the pregnancy. Information collected will include gestational dating, ultrasound report, records of maternal, fetal complications and pregnancy outcome.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.6.