



## CLINICAL STUDY PROTOCOL

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**Study Title:** A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults

**Sponsor:** Gilead Sciences, Inc.  
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Foster City, CA 94404

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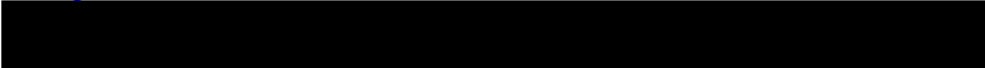
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## PROTOCOL SYNOPSIS

**Gilead Sciences, Inc.**  
**333 Lakeside Drive**  
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**Study Title:** A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults

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**IND Number:** 125,589  
**EudraCT Number:** 2015-003988-10  
**Clinical Trials.gov Identifier:** NCT02607956

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**Study Centers Planned:** Approximately 150 centers in North America, Europe, Latin America and Asia Pacific

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**Objectives:** The primary objective of this study is as follows:

- To evaluate the efficacy of a fixed dose combination (FDC) containing GS-9883/emtricitabine/tenofovir alafenamide (GS-9883/F/TAF) versus dolutegravir (DTG) + a FDC containing emtricitabine/tenofovir alafenamide (F/TAF) in HIV-1 infected, antiretroviral treatment-naïve adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

The secondary objective of this study is as follows:

- To evaluate the efficacy, safety and tolerability of the two treatment groups through Weeks 48, 96, and 144
- To evaluate the long term efficacy and safety of FDC GS-9883/F/TAF through open-label (OL) Weeks 48 and 96

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**Study Design:** Randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of GS-9883/F/TAF FDC versus DTG + F/TAF FDC in HIV-1 infected, antiretroviral treatment-naïve adult subjects. Subjects who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to one of the following two treatment groups:

**Treatment Group 1:** FDC of GS-9883 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) + Placebo to match dolutegravir 50 mg and Placebo to match FDC of emtricitabine 200 mg/tenofovir alafenamide 25 mg (F/TAF) administered orally, once daily, without regard to food (n=300)

**Treatment Group 2:** Dolutegravir 50 mg + FDC of emtricitabine 200 mg/tenofovir alafenamide 25 mg (F/TAF) + Placebo to match FDC of GS-9883 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (GS-9883/F/TAF) administered orally, once daily, without regard to food (n=300)

Randomization will be stratified by HIV-1 RNA level (< 100,000 copies/mL, > 100,000 to < 400,000 copies/mL, or > 400,000 copies/mL) at screening, CD4+ cell count (< 50 cells/ $\mu$ L, 50 – 199 cells/ $\mu$ L, or  $\geq$  200 cells/ $\mu$ L) at screening, and region (US vs. Ex-US) at randomization.

Number of Subjects Planned:	Approximately 600 subjects in total. 300 subjects in each Treatment Group 1 and Treatment Group 2
Target Population:	Antiretroviral treatment-naïve (except the use for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP), up to one month prior to screening), HIV-1 infected adults with plasma HIV-1 RNA levels $\leq$ 500 copies/mL and a screening genotype showing sensitivity to FTC and tenofovir (TFV).
Duration of Treatment:	Subjects will be treated for at least 144 weeks during the blinded treatment phase. After Week 144, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit. Once the last subject completes the Week 144 visit and Gilead completes the Week 144 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, subjects will be given GS-9883/F/TAF FDC in an open label (OL) extension phase for 96 weeks (Week 96 OL). After Week 96 OL, subjects will discontinue the study drug, transition onto commercially available treatment and complete a 30-Day Follow-up Visit. In a country where GS-9883/F/TAF is not available, subjects will be given the option to continue OL GS-9883/F/TAF until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

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

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

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

Diagnosis and Main Eligibility Criteria:

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

- Plasma HIV-1 RNA levels < 500 copies/mL at screening
- Antiretroviral treatment naïve ( < 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection) except the use for PrEP or PEP, up to one month prior to screening.
- Screening genotype report must show sensitivity to FTC and TFV
- Estimated GFR > 30 mL/min according to the Cockcroft-Gault formula for creatinine clearance

Study Procedures/  
Frequency:

After screening procedures, eligible subjects will be randomized 1:1 to Treatment Group 1 or Treatment Group 2 and treated for 144 weeks. Following the Day 1 visit, subjects will be required to return for study visits at Weeks 4, 8, and 12, and then every 12 weeks from Week 12 through Week 144. After 144 weeks, all subjects will continue to take their blinded study drugs and attend study visits every 12 weeks until the End of Blinded Treatment Visit. All subjects participating in the open label extension phase, without regard to their blinded treatment regimen, will return for study visits at Week 12 OL and every 12 weeks thereafter for at least 96 weeks

For all eligible subjects, blood will be collected at Day 1, Weeks 4, 8, 12, and then every 12 weeks through the End of Blinded Treatment Visit. Blood will also be collected at Week 12 OL and every 12 weeks thereafter for at least 96 weeks during open label extension phase Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count, and complete or symptom-directed physical examinations will be performed at the Screening, Day 1 and all subsequent study visits.

Adverse events and concomitant medications will be assessed at each visit.



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<b>Test Product, Dose, and Mode of Administration:</b>	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.
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<b>Reference Therapy, Dose, and Mode of Administration:</b>	Dolutegravir 50 mg + FDC of emtricitabine 200 mg/tenofovir alafenamide 25 mg (F/TAF) administered orally, once daily, without regard to food.
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**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 who achieve HIV-1 RNA < 50 copies/mL at Week 48 as defined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm

The secondary efficacy endpoints include:

- The proportion of subjects who achieve HIV-1 RNA < 50 copies/mL at Week 96 and 144 as defined by the US FDA-defined snapshot algorithm
- The proportion of subjects who achieve HIV-1 RNA < 20 copies/mL at Weeks 48, 96, and 144 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in log<sub>10</sub> HIV-1 RNA and in CD4+ cell count at Weeks 48, 96, and 144
- The proportion of subjects who achieve HIV-1 RNA < 50 copies/mL at Weeks 48 OL and 96 OL as defined by Missing = Excluded and Missing = Failure algorithm
- The change from baseline in CD4+ cell count at Weeks 48 OL and 96 OL.

Pharmacokinetics: An intensive pharmacokinetic (PK) substudy will be performed at the Weeks 4 or 8 visits in a subset of subjects (target n=30) at study sites able to conduct this testing.

For all subjects on study drug, a single anytime pre or post-dose PK blood sample will be collected at Weeks 8, 24, and 36.

For all subjects on study drug, a trough PK blood sample will be obtained 20-28 hours following the last dose at Weeks 4 and 12.

Following an observed dose, one post-dose PK blood sample will be collected between 1 and 4 hours post-dose.

For intensive PK substudy, the following PK parameters for GS-9883 may be explored as applicable:

$C_{max}$ ,  $T_{max}$ ,  $C_{last}$ ,  $T_{last}$ ,  $C_{tau}$ ,  $T_{1/2}$ ,  $AUC_{tau}$ ,  $AUC_{0-last}$ ,  $Vz/F$ ,  $CL_{ss/F}$ .

The concentration of GS-9883 may be summarized using descriptive statistics. The pharmacokinetics of GS-9883 may be evaluated using population approaches. TAF and FTC concentrations may be analyzed and PK may be summarized as applicable.

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<b>Patient Reported Outcomes:</b>	Short Form 36 Health Survey (SF-36), HIV Symptoms Distress Module, Work Productivity and Activity Impairment Questionnaire (WPAI) and Pittsburgh Sleep Quality Index (PSQI) will be administered at Day 1, Weeks 4, 12 and 48.
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<b>Statistical Methods:</b>	<p>The primary analysis will consist of a non-inferiority test of GS-9883/F/TAF versus DTG + F/TAF, with respect to the proportion of subjects who achieve HIV-1 RNA &lt; 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm.</p> <p>It will be concluded that GS-9883/F/TAF is non-inferior to DTG + F/TAF if the lower bound of the 2-sided 95% confidence interval (CI) of the difference (GS-9883/F/TAF – DTG + F/TAF) in the response rate (HIV-1 RNA &lt; 50 copies/mL as defined by the</p>
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US FDA-defined snapshot algorithm) is greater than -12%; i.e., a margin of 12% is applied to non-inferiority assessment. The 95% CI will be constructed using a normal approximation method based on stratified Mantel-Haenszel proportions, where stratification factors include baseline HIV-1 RNA level ( $\leq 100,000$  copies/mL, vs.  $> 100,000$  copies/mL) and region (US vs. Ex-US).

The proportion of subjects who achieve HIV-1 RNA  $< 50$  copies/mL at Weeks 96 and 144 and the proportion of subjects who achieve HIV-1 RNA  $< 20$  copies/mL at Weeks 48, 96, and 144 as defined by the US FDA-defined snapshot algorithm will also be summarized. The 95% CIs will be constructed in the same manner as described for the primary efficacy endpoint.

The change from baseline in  $\log_{10}$  HIV-1 RNA and CD4+ cell count at Weeks 48, 96, and 144 will be summarized using descriptive statistics. The differences and the associated 2-sided 95% CIs will be constructed using an Analysis of Variance (ANOVA) model, including treatment (GS-9883/F/TAF vs. DTG + F/TAF), baseline HIV-1 RNA level ( $\leq 100,000$  copies/mL vs.  $> 100,000$  copies/mL), and region (US vs. Ex-US) as fixed effects in the model.

The proportion of subjects who achieve HIV-1 RNA  $< 50$  copies/mL at Weeks 48 OL and 96 OL will be summarized, where missing HIV-1 RNA will be excluded and treated as failure, respectively. The changes from baseline in CD4+ cell count and percentage at Weeks 48 OL and 96 OL will be summarized using descriptive statistics.

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

A total of approximately 600 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 treatment groups (300 subjects per treatment group), achieves at least 95% power to detect a non-inferiority margin of 12% in Week 48 response rate (HIV-1 RNA  $< 50$  copies/mL as defined by the US FDA-defined snapshot algorithm) difference between the 2 treatment groups. For the sample size and power computation, it is assumed that both treatment groups have a response rate of 91% (based on Gilead Studies GS-US-292-0104 and GS-US-292-0111), that the non-inferiority margin is 12%, and that the significance level of the test is at a one-sided 0.025 level.

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

## GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
BID	twice a day
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL <sub>cr</sub>	creatinine clearance
C <sub>max</sub>	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COBI, /co	cobicistat (GS-9350)
C <sub>tau</sub>	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
DTG	dolutegravir, Tivicay®
ECG	electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
FAS	full analysis set
EVG	elvitegravir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, Stribild®
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination
FTC/TAF	emtricitabine/tenofovir alafenamide

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

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

## 1. INTRODUCTION

### 1.1. Background

Human immunodeficiency virus-1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest around the world. There are approximately 2.4 million people in North America and Western and Central Europe living with HIV-1 and 36 million people worldwide. The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2014. The infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function, ultimately resulting in death. Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral therapy (HAART); the introduction of HAART was associated with a dramatic decrease in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality {[Mocroft 1998](#), [Palella 1998](#), [Sterne 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 {[Aldir 2014](#), [Sterrantino 2012](#)}

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

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

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

## **1.2. GS-9883**

### **1.2.1. General Information**

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

### **1.2.2. Preclinical Pharmacology and Toxicology**

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

#### **1.2.2.1. Pharmacology**

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

GS-9883 is mainly metabolized by uridine 5'-diphospho-glucuronosyltransferase (UGT1A1) and CYP3A. GS-9883 does not inhibit major human CYP isoforms or UGT1A1 at concentrations up to 25  $\mu$ M. Consequently, GS-9883 is unlikely to be a clinically relevant inhibitor of these enzymes, and is not expected to inhibit the metabolic clearance of drugs metabolized by these enzymes. GS-9883 only modestly inhibits renal transporter OCT2 ( $IC_{50} = 0.42 \mu$ M). 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  $\mu\text{M}$  (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  $\mu\text{g}\cdot\text{h}/\text{mL}$  and 1931  $\mu\text{g}\cdot\text{h}/\text{mL}$ , 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  $\mu\text{g}\cdot\text{h}/\text{mL}$  and 1078  $\mu\text{g}\cdot\text{h}/\text{mL}$ , respectively).

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

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

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

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

### **1.2.3. Clinical Trials of GS-9883**

Clinical trials entailing the use of GS-9883 include:

- GS-US-141-1218, a Phase 1 double blind, randomized, placebo-controlled, first-in-human, single- and multiple-ascending dose study evaluating the safety, tolerability, and PK of oral GS-9883 in healthy subjects and a randomized, open-label, 2-cohort, 3-period, crossover, PK study evaluating the drug interaction potential between F/TAF FDC tablet and GS-9883 in healthy subjects (completed)
- GS-US-141-1219, a Phase 1b randomized, double-blinded, sequential cohort placebo-controlled study of the safety, PK, and antiviral activity of GS-9883 in HIV-1 infected subjects (5 mg, 25 mg, 50 mg, 100 mg) (completed)
- GS-US-141-1233, a Phase 1, Open-label, Two-Cohort, Multiple-Period, Fixed-Sequence, Crossover Study to Evaluate 1) the Relative Bioavailability of Two GS-9883/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets Versus a GS-9883 (75 mg) Tablet and a Emtricitabine/Tenofovir Alafenamide (200/25 mg) Fixed-Dose Combination Tablet Administered Simultaneously and 2) the Effect of Food on the Pharmacokinetics of GS-9883, Emtricitabine and Tenofovir Alafenamide When Administered as GS-9883/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets (completed)
- GS-US-141-1478, a Phase 1, Open Label, Parallel Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of GS-9883 in Subjects with Normal and Impaired Hepatic Function (in life portion completed)
- GS-US-141-1479, a Phase 1, open-label, parallel-group, adaptive single-dose study to evaluate the PK of GS-9883 in subjects with normal and impaired renal function (completed)
- GS-US-141-1480, a Phase 1 partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of GS-9883 on the QT/QTc interval in healthy subjects (completed)
- GS-US-141-1481, a Phase 1 study to evaluate the pharmacokinetics, metabolism, and excretion of GS-9883 in healthy subjects (completed)

- GS-US-141-1485, a Phase 1 adaptive study to evaluate transporter, CYP-mediated and UGT1A1 drug-drug interactions between GS-9883 and probe drugs (completed)
- GS-US-141-1487, a Phase 1 randomized, Blinded, Placebo-Controlled Phase 1 Study Evaluating the Effect of GS-9883 on Renal Function as Assessed by Markers of Glomerular Filtration Rate (completed)
- GS-US-311-1790, a Phase 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-380-1991, a Phase I Single and Multiple Dose Study Evaluating the Pharmacokinetics, Safety, and Tolerability of GS-9883/Emtricitabine/Tenofovir Alafenamide Fumarate (GS-9883/FTC/TAF) in Healthy Japanese and Caucasian Subjects (ongoing)
- GS-US-380-1999, a Phase 1 Multiple Dose Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between GS-9883/Emtricitabine/Tenofovir Alafenamide Fumarate and Sofosbuvir/Velpatasvir/GS-9857 in Healthy Subjects (completed)
- GS-US-380-3908, a Phase 1, Blinded, Placebo-controlled, Two-period Crossover Drug Interaction Study to Assess the Effect of GS-9883/F/TAF on Metformin Pharmacokinetics in Healthy Subjects (completed)
- GS-US-380-3909, a Phase 1, Open Label, Multiple-Cohort, Multiple-Period, Fixed-Sequence, Drug Interaction Study to Evaluate the Effect of Antacid and Mineral Supplements on GS-9883 Pharmacokinetics (completed)
- GS-US-141-1475, a Phase 2 Randomized, Double-Blinded Study of the Safety and Efficacy of GS-9883 + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults (ongoing)

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

### 1.2.3.1. Phase 1 Safety and Pharmacokinetics

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

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

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

Changes 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)**

<b>GS-9883 PK Parameter Mean (%CV)</b>	<b>5mg (N=6)</b>	<b>25 mg (N=6)</b>	<b>50 mg (N=6)</b>	<b>100 mg (N=6)</b>	<b>300 mg (N=6)</b>	<b>600 mg (N=6)</b>
$C_{max}$ (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) <sup>a</sup>	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 <sub>0-24</sub> (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 <sub>max</sub> (ng/mL)	709.7 (9.5)	2220.0 (35.6)	4648.3 (18.7)	6248.3 (26.8)	13,716.7 (19.1)
	T <sub>max</sub> (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 <sub>tau</sub> (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 <sub>max</sub> (ng/mL)	982.5 (7.9)	3455.0 (24.1)	6538.3 (17.6)	9396.7 (20.8)	19,900.0 (21.2)
	C <sub>tau</sub> (ng/mL)	400.83 (26.9)	1322.00 (27.8)	2241.67 (28.2)	3145.00 (26.1)	6758.33 (21.6)
	T <sub>max</sub> (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<sub>max</sub>, and t<sub>1/2</sub>, which are presented as median (Q1, Q3)

Table 1-3 presents the GLSM ratios and associated 90% CIs for the test (fed) versus reference (fasted) treatments for the primary plasma PK parameters of GS-9883. Administration of a single dose of GS-9883 100 mg with food (high-calorie/high-fat breakfast) increased the GLSM values of C<sub>max</sub> and AUC<sub>inf</sub> 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<sub>1/2</sub> 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 <sub>inf</sub> (hr*ng/mL)	214,146.3 (15.9)	117,777.1 (23.3)	183.97 (152.05, 222.59)
AUC <sub>last</sub> (hr*ng/mL)	209,259.9 (15.1)	115,681.7 (24.0)	183.58 (151.91, 221.86)
C <sub>max</sub> (ng/mL)	11,268.8 (15.1)	5885.0 (34.9)	200.69 (165.93, 242.74)

CI = confidence interval; GLSM = geometric least squares mean

### 1.2.3.2. Phase 1b Proof of Concept

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

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

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

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

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

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

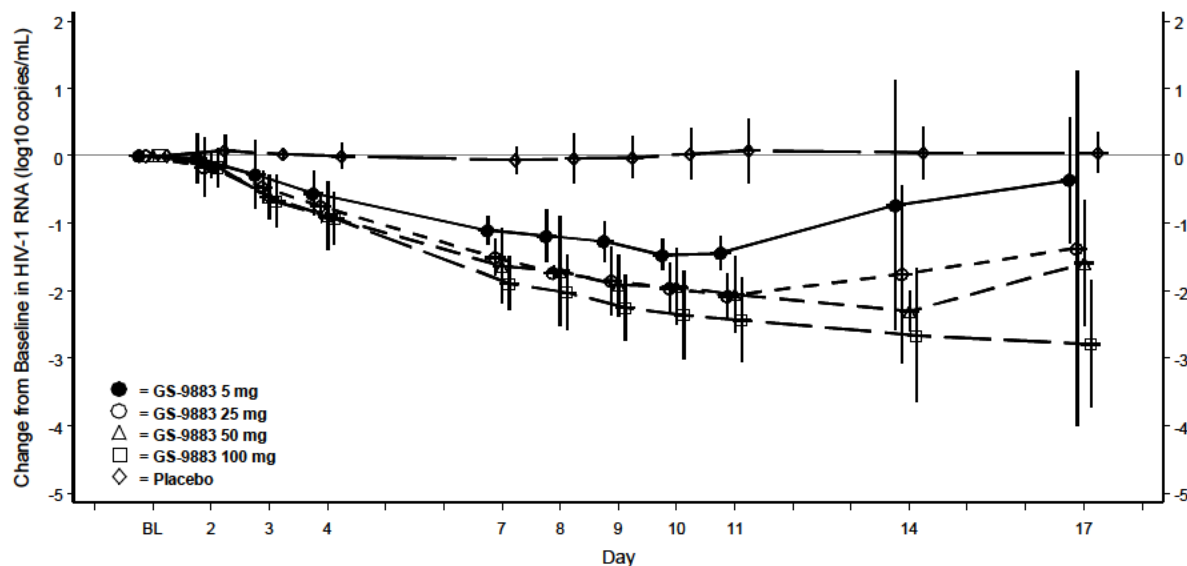
**Table 1-4. Trough GS-9883 Plasma Concentrations at Steady State Following GS-9883 Administration Under Fasting Conditions and Corresponding Protein-Adjusted IQ<sub>95</sub> Values (GS-9883 PK Analysis Set)**

GS-9883 dose	n	Median (range) C <sub>tau, SS</sub> (ng/mL)	Median (range) paIQ <sub>95</sub> <sup>a</sup>
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)

<sup>a</sup> The protein adjusted IQ<sub>95</sub> (paIQ<sub>95</sub>) value is estimated based on steady-state C<sub>tau</sub> values and the in vitro paIC<sub>95</sub> value for wild-type HIV-1 (162 ng/ml).

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

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



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

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

Mean viral load change on Day 11 was  $-2.08 \log_{10}$  in the 25 mg cohort,  $-2.06 \log_{10}$  in the 50 mg cohort, and  $-2.43 \log_{10}$  in the 100 mg cohort. Time weighted average change from baseline at Day 11 (DAVG11) was  $-0.92 \log_{10}$  in the 5 mg cohort,  $-1.33 \log_{10}$  in the 25 mg cohort,  $-1.37 \log_{10}$  in the 50 mg cohort and  $-1.61 \log_{10}$  in the 100 mg cohort. Viral suppression (HIV-1 RNA  $< 50$  copies/mL) was ever achieved by the end of the study (Day 17) by 1 subject (25.0%) in the GS-9883 50 mg group and 2 subjects (50%) in the GS-9883 100 mg group.

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

Study GS-US-141-1475 is an ongoing Phase 2, randomized, double-blind, multicenter, active-controlled study to assess the safety and efficacy of a regimen containing GS-9883+F/TAF versus dolutegravir (DTG)+F/TAF in HIV-infected, ART-naïve 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  $\leq 400,000$  copies/mL, or  $> 400,000$  copies/mL) at screening:

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

Week 24 interim data are summarized below.

### ***Subject Disposition and Baseline Characteristics***

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

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

Key baseline disease characteristics (ie, viral load, CD4 cell count, and eGFR<sub>CG</sub>) were similar between the 2 treatment groups.

Median (first quartile [Q1], third quartile [Q3]) baseline HIV-1 RNA was 4.45 (3.96, 4.79) log<sub>10</sub> copies/mL, with 82.7% of subjects having  $\leq 100,000$  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/ $\mu$ L, with 41.8% of subjects having  $\leq 500$  cells/ $\mu$ L at baseline. Median (Q1, Q3) baseline eGFR<sub>CG</sub> was 125.3 (105.7, 147.0) mL/min.

### ***Efficacy Results***

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

Of the 5 subjects with baseline viral load  $> 400,000$  copies/mL, 4 had HIV-1 RNA  $< 50$  copies/mL at Week 24, and 1 had 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/ $\mu$ L; DTG+F/TAF 507 (271.0) cells/ $\mu$ L;  $p = 0.35$ . 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/ $\mu$ L; DTG+F/TAF, +173 (220.5) cells/ $\mu$ L (difference in least squares mean [LSM]: 0; 95% CI: -76 to 76;  $p = 1.00$ ). There were similar increases in the mean (SD) CD4 cell count in both treatment groups Week 24: GS-9883+F/TAF, +189 (177.8) cells/ $\mu$ L; DTG+F/TAF, +157 (163.2) cells/ $\mu$ L (difference in LSM: 39; 95% CI: -35 to 113;  $p = 0.30$ ).

#### *Interim Virology Resistance Data*

Through Week 24, no emergent drug resistance was detected.

#### ***Safety Results***

##### *Adverse Events*

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

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

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

The overall incidence of study drug-related treatment-emergent AEs was balanced between treatment groups as follows: GS-9883+F/TAF 15.4%, 10 subjects; DTG+F/TAF 18.2%, 6 subjects. Most study drug-related treatment-emergent AEs were Grade 1 in severity. Grade 2 study drug-related treatment-emergent AEs were reported in 1 subject in the GS-9883+F/TAF group (somnolence and headache) and 1 subject in the DTG+F/TAF group (vomiting). There were no Grade 3 or 4 treatment-emergent AEs or SAEs reported that were considered related to study drug.

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

### *Clinical Laboratory Evaluations*

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

There were no clinically significant changes from baseline or differences between treatment groups in the median values for hematology, chemistry, or metabolic parameters. There were similar increases from baseline in median (Q1, Q3) serum creatinine in both treatment groups at Week 24: GS-9883+F/TAF 0.12 (0.06, 0.18) mg/dL; DTG+F/TAF 0.13 (0.05, 0.21) mg/dL. There were decreases in median (Q1, Q3) eGFR<sub>CG</sub> 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/ $\mu$ L; DTG+F/TAF, +157 (163.2) cells/ $\mu$ L (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<sup>®</sup>, 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 ARV drugs. The 200 mg FTC capsule formulation was approved by the US FDA for marketing on 2 July 2003 and is available under the name Emtriva<sup>®</sup>. In the European Union (EU), marketing authorization was granted for both the 200 mg Emtriva<sup>®</sup> capsule formulation and a 10 mg/mL Emtriva<sup>®</sup> 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<sup>®</sup>.

### **1.4. Information about Tenofovir Alafenamide (TAF, GS-7340)**

Tenofovir alafenamide (GS-7340, TAF) is a second generation oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP), a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the elongation of the viral DNA chain. The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV.

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

#### **1.4.1. Clinical Trials of Single Agent Tenofovir Alafenamide (TAF, GS-7340) or Fixed Dose Combination Emtricitabine/Tenofovir Alafenamide (FTC/TAF)**

Clinical trials entailing the use of tenofovir alafenamide include:

- GS-US-120-1101, a Phase 1/2 study of the pharmacokinetics and antiviral activity of GS-7340 (50 mg and 150 mg) in HIV-infected subjects (completed)
- GS-US-120-0104, a Phase 1b study of the pharmacokinetics and antiviral activity of GS-7340 (8 mg, 25 mg, 40 mg) in HIV infected subjects (completed)

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

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

#### **1.4.2. Clinical Trials of FTC/TAF as part of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF)**

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

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

- GS-US-292-0119, a Phase 3 open-label study to evaluate switching from optimized stable antiretroviral regimens containing darunavir to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) single tablet regimen (STR) plus darunavir (DRV) in treatment experienced HIV-1 positive adults (ongoing)
- GS-US-292-0106, a Phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected antiretroviral treatment-naïve 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-naïve 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-naïve 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: Study of the Relative Bioavailability of GS-9883, FTC, and TAF between GS-9883/F/TAF and GS-9883 + F/TAF**

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

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

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

#### **Cohort 1 Results:**

- Pharmacokinetic Results Under fasted conditions, GS-9883 AUC<sub>inf</sub> and C<sub>max</sub> 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<sub>inf</sub> and a 27% higher GS-9883 C<sub>max</sub>. The impact of food on TAF and FTC exposure was similar to that previously observed for F/TAF (Study GS-US-311-1386). GS-9883/F/TAF may be taken without regard to food. Based on these results, Cohort 2 was added to the study via protocol amendment to evaluate the relative BA of the GS-9883/F/TAF (50/200/25 mg) FDC tablet compared with the single-agent GS-9883 (75 mg) tablet and the F/TAF (200/25 mg) FDC tablet administered simultaneously.

#### **Safety Results**

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



## **Cohort 2 Results:**

### **Pharmacokinetic Results**

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

### **Safety Results**

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

#### **1.6. Information about Dolutegravir (DTG, Tivicay®)**

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

#### **1.7. Rationale for this Study**

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

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

The objective of this study is to evaluate the safety and efficacy of a FDC containing GS-9883/F/TAF versus DTG + a FDC of F/TAF. Dolutegravir is a second generation, unboosted INSTI, providing a once daily unboosted option with rapid viral suppression, good tolerability, and a high barrier to resistance and is on the DHHS Treatment Guidelines as a preferred INSTI. By keeping the backbone of F/TAF constant in both arms, we will be able to compare GS-9883 with DTG in a single variable design trial. This design is an extension of the ongoing Phase 2 study, given that a single variable design is considered the best direct evidence of benefit.

### **1.8. Risk/Benefit Assessment for the Study**

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

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

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 and DTG + F/TAF is favorable at this time.

## 1.9. Rationale for Dose Selection

### FTC

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

### TAF

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

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

### GS-9883

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

**Table 1-5. GS-US-141-1219: Trough GS-9883 Plasma Concentrations at Steady State Following GS-9883 Administration Under Fasting Conditions and Corresponding Protein-Adjusted IQ<sub>95</sub> Values**

GS-9883 dose	n	Median (range) C <sub>tau,SS</sub> (ng/mL)	Median (range) paIQ <sub>95</sub> <sup>a</sup>
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<sub>95</sub> value is estimated based on steady-state C<sub>tau</sub> values and the in vitro paIC<sub>95</sub> 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<sub>95</sub>) 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<sub>95</sub> 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<sub>95</sub> of approximately 20, providing considerable coverage above the target concentration of 162 ng/mL (paIC<sub>95</sub>). GS-9883 (75 mg) single agent coadministered with F/TAF (200/25 mg) is currently being evaluated in a Phase 2 study, GS-US-141-1475 (GS-9883+F/TAF vs DTG+F/TAF). The Week 24 data from this study support the safety and efficacy of GS-9883 exposures obtained with the 75 mg dose of the single agent.

### **GS-9883/F/TAF FDC Dose Selection**

A fixed dose formulation of GS-9883/F/TAF was developed for use in Phase 3 studies. Preliminary results from the relative bioavailability (rBA) study (GS-US-141-1233) of GS-9883/F/TAF (75/200/25 mg) showed that GS-9883 plasma exposure was higher (with  $C_{\max}$  and AUC<sub>inf</sub> 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<sub>95</sub> of 24.3, compared to an estimated mean paIQ<sub>95</sub> of 19.2 for the GS-9883 (75 mg) single agent coadministered with F/TAF, in the fasted state.

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

#### **1.10. Compliance**

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

## 2. OBJECTIVES

The primary objective of this study is:

- To evaluate the efficacy of a fixed dose combination (FDC) containing GS-9883/emtricitabine/tenofovir alafenamide (GS-9883/F/TAF) versus dolutegravir (DTG) + a FDC containing emtricitabine/tenofovir alafenamide (F/TAF) in HIV-1 infected, antiretroviral treatment-naïve adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

The secondary objective of this study is:

- To evaluate the efficacy, safety and tolerability of the two treatment regimens through Weeks 48, 96, and 144

To evaluate the long term efficacy and safety of FDC GS-9883/F/TAF through OL Weeks 48 and 96.

### 3. STUDY DESIGN

#### 3.1. Endpoints

The primary endpoint is:

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

The secondary endpoints of this study include:

- The proportion of subjects who achieve HIV-1 RNA < 50 copies/mL at Weeks 96 and 144 as defined by the US FDA-defined snapshot algorithm
- The proportion of subjects who achieve HIV-1 RNA < 20 copies/mL at Weeks 48, 96, and 144 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in log<sub>10</sub> HIV-1 RNA and CD4+ cell count at Weeks 48, 96, and 144
- The proportion of subjects who achieve HIV-1 RNA < 50 copies/mL at Weeks 48 OL and 96 OL as defined by Missing = Excluded and Missing = Failure algorithm
- The change from baseline in CD4+ cell count at Weeks 48 OL and 96 OL.

#### 3.2. Study Design

This protocol describes a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of GS-9883/F/TAF FDC versus DTG + FDC of FTC/TAF in HIV-1 infected, antiretroviral treatment-naïve adult subjects.

#### 3.3. Study Treatments

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

**Treatment Group 1:** FDC of GS-9883 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) + Placebo to match dolutegravir 50 mg and Placebo to match FDC of emtricitabine 200 mg/tenofovir alafenamide 25 mg (F/TAF) administered orally, once daily, without regard to food (n=300)

**Treatment Group 2:** Dolutegravir 50 mg + FDC of emtricitabine 200 mg/tenofovir alafenamide 25 mg (F/TAF) + Placebo to match FDC of GS-9883 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (GS-9883/F/TAF) administered orally, once daily, without regard to food (n=300)

Randomization will be stratified by HIV-1 RNA level ( ≤ 100,000 copies/mL, > 100,000 to 400,000 copies/mL, or > 400,000 copies/mL) at screening, CD4+ cell count (< 50 cells/μL, 50 - 199 cells/μL, or ≥ 200 cells/μL) at screening, and region (US vs. Ex-US) at randomization.

### **3.4. Duration of Treatment**

Subjects will be treated for at least 144 weeks during the blinded treatment phase. After Week 144, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit. Once the last subject completes the Week 144 visit and Gilead completes the Week 144 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, subjects will be given GS-9883/F/TAF FDC in an open label (OL) extension phase for 96 weeks (Week 96 OL). After Week 96 OL, subjects will discontinue the study drug, transition onto commercially available treatment and complete a 30-Day Follow-up Visit. In a country where GS-9883/F/TAF is not available, subjects will be given the option to continue OL GS-9883/F/TAF until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

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

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

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





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[REDACTED]

## 4. SUBJECT POPULATION

### 4.1. Number of Subjects and Subject Selection

Approximately 600 subjects who meet the eligibility criteria will be enrolled.

### 4.2. Inclusion Criteria

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

- 1) The ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures
- 2) Age  $\geq$  18 years
- 3) Antiretroviral treatment naïve (  $\leq$  10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection) except the use for PrEP (pre-exposure prophylaxis) or PEP (post-exposure prophylaxis), up to one month prior to screening
- 4) Plasma HIV-1 RNA levels  $\geq$  500 copies/mL at screening
- 5) Normal ECG (or if abnormal, determined by the Investigator to be not clinically significant)
- 6) Adequate renal function:  
Estimated glomerular filtration rate  $\geq$  30 mL/min (  $\geq$  0.50 mL/sec) according to the Cockcroft-Gault formula {[Cockcroft 1976](#)}:  
  
Male: 
$$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = \text{CLcr (mL/min)}$$
$$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in umol/L}) \times 0.6786} = \text{CLcr (mL/sec)}$$
  
Female: 
$$\frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})} = \text{CLcr (mL/min)}$$
$$\frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in umol/L}) \times 0.6786} = \text{CLcr (mL/sec)}$$
- 7) Hepatic transaminases (AST and ALT)  $\leq$  5  $\times$  upper limit of normal (ULN)
- 8) Total bilirubin  $\leq$  1.5 mg/dL ( $\leq$  26 umol/L), or normal direct bilirubin

- 9) Adequate hematologic function (absolute neutrophil count  $> 750/\text{mm}^3$  ( $> 0.75 \text{ GI/L}$ ); platelets  $> 50,000/\text{mm}^3$  ( $> 50 \text{ GI/L}$ ); hemoglobin  $> 8.5 \text{ g/dL}$  ( $> 85 \text{ g/L}$ ))
- 10) Serum amylase  $> 5 \times \text{ULN}$  (subjects with serum amylase  $> 5 \times \text{ULN}$  will remain eligible if serum lipase is  $> 5 \times \text{ULN}$ )
- 11) Females of childbearing potential must agree to utilize protocol recommended highly effective contraceptive methods or be non-heterosexually active or practice sexual abstinence (as defined in [Appendix 7](#)) from screening, throughout the duration of the study period, and for 30 days following the last dose of study drug.
  - a) Female subjects who utilize hormonal contraceptive as one of their birth control methods must have used the same method for at least 3 months prior to study drug dosing.
- 12) Male subjects who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception (as described in [Appendix 7](#)) throughout the study period and for 90 days following the last dose of study drug.
- 13) Male subjects must agree to refrain from sperm donation from first study drug dose until at least 90 days following the last study drug dose
- 14) Life expectancy  $> 1$  year
- 15) Screening genotype report must show sensitivity to FTC and TFV. This report will be provided by Gilead Sciences. Alternatively, if genotype results from a local laboratory obtained  $> 90$  days prior to screening visit date show sensitivity to these drugs, this genotype will be acceptable to fulfill this inclusion criterion in the event that the genotype obtained at screening is not yet available and all other inclusion/exclusion criteria have been confirmed

#### **4.3. Exclusion Criteria**

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

- 1) An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening (refer to [Appendix 6](#))
- 2) Subjects experiencing decompensated cirrhosis (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 other clinical trial, including observational studies, without prior approval from the sponsor is prohibited while participating in this trial
- 8) Any other clinical condition or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with the dosing requirements
- 9) Any known allergies to the excipients of GS-9883/F/TAF FDC or DTG + F/TAF FDC tablets
- 10) Females who are pregnant (as confirmed by positive serum pregnancy test)
- 11) Females who are breastfeeding
- 12) Subjects receiving ongoing therapy with any of the following medications in the table below, including drugs not to be used with FTC, TAF, GS-9883 and DTG

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

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

- 13) Acute hepatitis in the 30 days prior to study entry
- 14) Screening HBV DNA with HBV viral load > 9 log IU/mL, if determined to be HBV infected
- 15) Active tuberculosis infection

## 5. INVESTIGATIONAL MEDICINAL PRODUCTS

### 5.1. Randomization, Blinding and Treatment Codes

Subjects will be assigned a screening number at the time of consent. **Randomization and Day 1 visits cannot occur until the Investigator has received the results of the screening genotype report and 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.

Randomization will be stratified by HIV-1 RNA level ( $\leq 100,000$  copies/mL,  $> 100,000$  to  $400,000$  copies/mL, or  $> 400,000$  copies/mL) at screening, CD4+ cell count ( $< 50$  cells/ $\mu$ L,  $50 - 199$  cells/ $\mu$ L, or  $\geq 200$  cells/ $\mu$ L) at screening and region (US vs. Ex-US) at randomization.

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

At the End of Blinded Treatment Visit the IWRS will assign open label GS-9833/F/TAF/FDC

#### 5.1.1. Procedures for Breaking Treatment Codes

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

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

Gilead Pharmacovigilance and Epidemiology (PVE) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

## 5.2. Description and Handling

### 5.2.1. Formulation

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

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

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

#### 5.2.1.2. Dolutegravir (DTG) 50 mg and Placebo to Match Tablets

Dolutegravir 50 mg tablets are round, film-coated yellow, debossed with "50" on one side and debossed with "SV 572" on the other side. Each tablet core contains 50 mg of dolutegravir. In addition to the active ingredient, DTG tablets contain D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate and sodium stearyl fumarate. The tablet cores are film-coated with iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

The placebo to match (PTM) DTG tablets are round, film coated yellow, debossed with "50" on one side and debossed with "SV 572" on the other side. PTM DTG tablets are identical in physical appearance to DTG 50 mg tablets. The placebo tablet cores contain microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate. The tablet cores are film-coated with iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

#### 5.2.1.3. Emtricitabine/Tenofovir alafenamide (F/TAF) 200 mg/25 mg and Placebo to Match Tablets

Emtricitabine 200 mg/tenofovir alafenamide 25 mg tablets are rectangular-shaped, film-coated blue, debossed with "GSI" on one side of the tablet and "225" on the other side of the tablet. Each tablet core contains 200 mg of emtricitabine and 25 mg of tenofovir alafenamide. In addition to the active ingredients, the F/TAF tablets contain croscarmellose sodium, magnesium stearate and microcrystalline cellulose. The tablet cores are film-coated with FD&C blue #2/indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

The placebo to match (PTM) F/TAF tablets are rectangular-shaped, film-coated blue, debossed with "GSI" on one side of the tablet and "225" on the other side of the tablet. PTM F/TAF tablets are identical in physical appearance to F/TAF 200 mg/25 mg tablets. The placebo tablet cores contain microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate. The tablet cores are film-coated with FD&C blue #2/indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

### **5.2.2. Packaging and Labeling**

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

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

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

#### **5.2.2.2. Dolutegravir (DTG) 50 mg and Placebo to Match Tablets**

Dolutegravir 50 mg tablets and PTM Dolutegravir 50 mg tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

#### **5.2.2.3. Emtricitabine/Tenofovir Alafenamide (F/TAF) 200 mg/25 mg and Placebo to Match Tablets**

Emtricitabine/tenofovir alafenamide (F/TAF) 200 mg/25 mg and Placebo to Match tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

### **5.2.3. Storage and Handling**

Study drugs should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

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

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

### **5.3. Dosage and Administration of GS-9883/Emtricitabine/Tenofovir alafenamide and Dolutegravir + Emtricitabine/Tenofovir alafenamide**

Study drugs GS-9883/F/TAF FDC, DTG + F/TAF FDC and placebo-to-match tablets will be provided by Gilead Sciences.

**Treatment Group 1:** FDC of GS-9883 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) + Placebo to match dolutegravir 50 mg and Placebo to match FDC of emtricitabine 200 mg/tenofovir alafenamide 25 mg (F/TAF) administered orally, once daily, without regard to food

**Treatment Group 2:** Dolutegravir 50 mg + FDC of emtricitabine 200 mg/tenofovir alafenamide 25 mg (F/TAF) + Placebo to match FDC of GS-9883 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (GS-9883/F/TAF) administered orally, once daily, without regard to food.

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

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

##### 5.4.1. Prior and Concomitant Medications (Blinded Phase through End of Blinded Treatment Visit)

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

Medications listed in the following table and use of herbal/natural supplements are excluded or should be used with caution while subjects are participating in the study. Subjects will refrain from consumption of grapefruit juice and Seville orange juice throughout participation in the study.

**Table 5-1. Prior and Concomitant Medications (Blinded Phase through End of Blinded Treatment Visit)**

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 Roloids); the ulcer medication sucralfate (Carafate); or vitamin or mineral supplements that contain calcium, iron or zinc for a minimum of 6 hours before and 2 hours after any dose of study drug.
Antiarrhythmic Agent	Dofetilide	
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials	Rifampin, Rifapentine	
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen	
GI Motility Agents	Cisapride	
Herbal/Natural Supplements	St. John's Wort, Echinacea	
Oral Hypoglycemic Agent		Metformin: close monitoring is recommended. A dose adjustment of Metformin may be necessary. Limit total daily doses of Metformin to 1000 mg when initiating study medication or if initiating metformin while on study drug.

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

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

**5.4.2. Prior and Concomitant Medications (Open-Label Rollover Extension Phase)**

The use of medications for the treatment of HIV-1 infection, other than GS-9883/F/TAF, is prohibited.

Medications listed in the following table and use of herbal/natural supplements are excluded or should be used with caution while participants are participating in the study. This list should be utilized in jurisdictions in which GS-9883/F/TAF has NOT been approved.

**Table 5-2. Prior and Concomitant Medications (Open-Label Rollover Extension Phase)**

Drug Class	Agents Disallowed*	To Be Used With Caution
Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): Calcium or iron supplements Cation-containing antacids or laxatives Buffered medications		Antacids containing Al/Mg or Calcium: GS-9883/F/TAF can be taken under fasting conditions 2 hours before antacids containing Al/Mg or calcium.  Routine administration of GS-9883/F/TAF simultaneously with, or 2 hours after, antacids containing Al/Mg or calcium is not recommended.  Supplements containing Calcium or Iron: GS-9883/F/TAF and supplements containing calcium or iron can be taken together with food. Routine administration of GS-9883/F/TAF under fasting conditions simultaneously with, or 2 hours after, supplements containing calcium or iron is not recommended.
Antiarrhythmic Agent	dofetilide	
Anticonvulsants	phenobarbital, phenytoin, carbamazepine, oxcarbazepine	
Antimycobacterials	rifampin, rifapentine, rifabutin	
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen	
Hypoglycemic agent		Metformin: Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIKTARVY and metformin.
Herbal/Natural Supplements	St. John's Wort	

\* 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.

**In jurisdictions in which GS-9883/F/TAF has been approved, consult the local prescribing information for GS-9883/F/TAF dose recommendations with concomitant medications.**

Should participants have a need to initiate treatment with any excluded concomitant medication, the Gilead Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator must notify Gilead 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 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 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 (females of childbearing potential only). If the test is positive, the subject will not be enrolled

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

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

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

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

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

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

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

— CD4+ cell count

— Plasma HIV-1 RNA

— Hepatitis B Virus (HBV) blood panel: Hepatitis B virus surface antigen serology (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.

— HIV-1 genotype testing (protease and reverse transcriptase). The HIV-1 PR/RT genotype testing may not be performed for subjects that fail to meet other screening criteria.

- 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.

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 received the results from the screening genotype report and 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
- Short Form 36 Health Survey (SF-36), HIV Symptoms Distress Module, Work Productivity and Activity Impairment Questionnaire (WPAI) and Pittsburgh Sleep Quality Index (PSQI) to be completed by the subject. Subject is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will not be able to participate
  - Urine storage sample for possible additional clinical testing

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, phosphorus, magnesium, potassium, sodium, uric acid, amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) and TSH. PT/INR (prothrombin time/international normalized ratio)
  - 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 sample for safety, virology, or PK testing
  - 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.

█ [REDACTED]

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█ [REDACTED]

[REDACTED]

[REDACTED]

### 6.3. Randomization

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

### 6.4. Treatment Assessments (Week 4 -144)

The following evaluations are to be completed at the end of Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144 unless otherwise specified.

Study visits are to be completed within  $\pm 2$  days of the protocol-specified visit date based on the Day 1 visit through Week 12 and completed within  $\pm 6$  days of the protocol-specified visit date through Week 144, unless otherwise specified. The visit window at Weeks 48, 96 and 144 will be  $\pm 6$  weeks of the protocol-specified visit date, and these clinical visit windows coincide with the Weeks 48, 96 and 144 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, 48, 96, 144**) (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, 48, 96, 144**)
- Short Form 36 Health Survey (SF-36), HIV Symptoms Distress Module, Work Productivity and Activity Impairment Questionnaire (WPAI) and Pittsburgh Sleep Quality Index (PSQI) to be completed by the subject at **Weeks 4, 12 and 48**. Subject is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.



- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be discontinued
  - Urine storage sample for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase  $> 1.5 \times$  ULN). At Weeks 12, 24, 48, 72, 96, 120, and 144 analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. At Weeks 24, 48, 72, 96, 120 and 144, 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, 48, 72, 96, 120, and 144)**
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Plasma HIV-1 RNA
  - CD4+ cell count
  - Plasma storage sample for safety, virology, or PK testing
  - For subjects who meet the definition of HBV infection at any visit

The following will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative) and HBeAg (if negative, reflex HBeAb) **(Weeks 12, 24, 48, 72, 96 and every 24 weeks post Week 96)**

Plasma HBV DNA

— For subjects who do NOT meet the definition of HBV infection at any visit

The following will be conducted by the central laboratory: Hepatitis B surface antibody (HBsAb), Hepatitis B virus core antibody (HBcAb), and Hepatitis B virus surface antigen serology (HBsAg). Subjects who are HBsAg and/or HBcAb positive will have a reflex test for HBV DNA (viral load) (**Weeks 48, 96 and 144**)

— Hepatitis C virus (HCVAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed (**Weeks 48, 96 and 144**)

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

— **Single Anytime, Trough and Post Dose PK Samples for all subjects on study drug:**

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

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

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



- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- 12-lead ECG performed supine (**every 48 weeks**)
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be discontinued.
  - Urine storage sample for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase  $> 1.5 \times \text{ULN}$ ). Every 24 weeks, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. In addition, TSH will also be analyzed every 24 weeks.
  - Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments. (**Every 24 weeks**)
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Plasma HIV-1 RNA
  - CD4+ cell count
  - For subjects who meet the definition of HBV infection at any visit
    - The following will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative) and HBeAg (if negative, reflex HBeAb). (**every 24 weeks**)

Plasma HBV DNA

— For subjects who do NOT meet the definition of HBV infection at any visit

The following will be conducted by the central laboratory: Hepatitis B surface antibody (HBsAb), Hepatitis B virus core antibody (HBcAb), and Hepatitis B virus surface antigen serology (HBsAg). Subjects who are HBsAg and/or HBcAb positive will have a reflex test for HBV DNA (viral load) (**every 48 weeks**)

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

- Subjects who meet the criteria for virologic failure will be managed according to the Management of Virologic Rebound Sections 6.12.1 and 6.12.2.
- Document study drug dispensation and accountability for all study drugs dispensed.

### **6.5.2. End of Blinded Treatment Visit**

Once the last subject completes the Week 144 visit and Gilead completes the Week 144 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, subjects will be given GS-9883/F/TAF FDC in an open label (OL) extension phase for 96 weeks (Week 96 OL). After Week 96 OL, subjects will discontinue the study drug, transition onto commercially available treatment and complete a 30-Day Follow-up Visit. In a country where GS-9883/F/TAF is not available, subjects will be given the option to continue OL GS-9883/F/TAF until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first. Subjects who receive the open-label GS-9883/F/TAF FDC will return for study visits every 12 weeks.

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

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

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

- Review of AEs and changes in concomitant medications
- 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 pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will not be able to participate.
  - Urine storage sample for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase  $> 1.5 \times$  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 sample for safety, virology, or PK testing
  - Plasma HBV DNA (for subjects who meet the definition of HBV infection)
- Document study drug dispensation, if applicable, and accountability for all study drugs dispensed
- Subjects who wish to continue in the Open-Label Rollover extension study will receive open label GS-9883/F/TAF.

### 6.5.3. Treatment Assessments (Open-Label Rollover Extension)

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

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

Study visits are to be completed of the protocol-specified visit date based on the End of Blinded Treatment Visit through Week 12 OL and completed  $\pm$  6 days of the protocol-specified visit date every 12 weeks thereafter, unless otherwise specified.

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

- Review of AEs and changes in concomitant medications
- Complete physical examination (**Week 48 OL, Week 96 OL**) (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- 12-lead ECG performed supine (**Week 48 OL, Week 96 OL**)
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be discontinued.
  - Urine storage sample for possible additional clinical testing

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase  $> 1.5 \times$  ULN). At Weeks 24, 48, 72, and 96 OL, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. In addition, TSH will also be analyzed at Week 24, 48, 72 and 96 OL.
  - 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. **(Week 24, 48, 72 and 96 OL)**
  - 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
  - For subjects who meet the definition of HBV infection at any visit
    - The following will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative) and HBeAg (if negative, reflex HBeAb) **(every 24 weeks)**
    - Plasma HBV DNA **(every 12 weeks)**
  - For subjects who do NOT meet the definition of HBV infection at any visit
    - The following will be conducted by the central laboratory: Hepatitis B surface antibody (HBsAb), Hepatitis B virus core antibody (HBcAb), and Hepatitis B virus surface antigen serology (HBsAg). Subjects who are HBsAg and/or HBcAb positive will have a reflex test for HBV DNA (viral load) **(Week 48 and Week 96 OL)**
  - Hepatitis C virus (HCVAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed **(Week 48 and Week 96 OL)**
- Plasma storage sample for safety, virology, or PK testing
- Document study drug dispensation and accountability for all study drugs dispensed.
- Subjects who meet the criteria for virologic failure will be managed according to the Management of Virologic Rebound Section [6.12.1](#).



## 6.6. Post-treatment Assessments

### 6.6.1. Early Study Drugs Discontinuation Assessments

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

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

**At the Early Study Drugs Discontinuation Visit, any evaluations showing abnormal results indicating that 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 (blinded treatment phase only)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test
  - Urine storage sample for possible additional clinical testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN), and TSH

- Estimated glomerular filtration rate according to the Cockcroft-Gault formula
- Hematology profile: complete blood count (CBC) with differential and platelet count
- Plasma HIV-1 RNA
- CD4+ cell count
- Plasma storage sample for safety, virology, or PK testing
- Plasma HBV DNA (for subjects who meet the definition of HBV infection anytime)
- HIV-1 genotype/phenotype testing for subjects with virologic failure
- Drug accountability

### **6.6.2. 30 Day Follow Up**

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

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

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

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

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

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

- Review of AEs and changes in concomitant medications
- Symptom-directed physical examination

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

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

## **6.7. Criteria for Discontinuation of Study Treatment**

Study medication will be discontinued in the following instances:

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Pregnancy during the study; refer to [Appendix 7](#)
- Development of active tuberculosis infection

Study medication may be discontinued in the following instances:

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

#### **6.8. Blood and Urine Storage**

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

#### **6.9. 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.

#### **6.10. End of Study**

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

#### **6.11. 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.

#### **6.12. Virologic Failure**

Virologic failure is defined as virologic rebound or having HIV-1 RNA  $\geq 50$  copies/mL at study drug discontinuation, Week 48, Week 96, Week 144, Week 48 OL or Week 96 OL.

### 6.12.1. Management of Virologic Rebound

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

- At any visit, after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA 50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit; OR
- At any visit, a > 1 log<sub>10</sub> increase in HIV-1 RNA from the nadir which is subsequently confirmed at the following scheduled or unscheduled visit

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

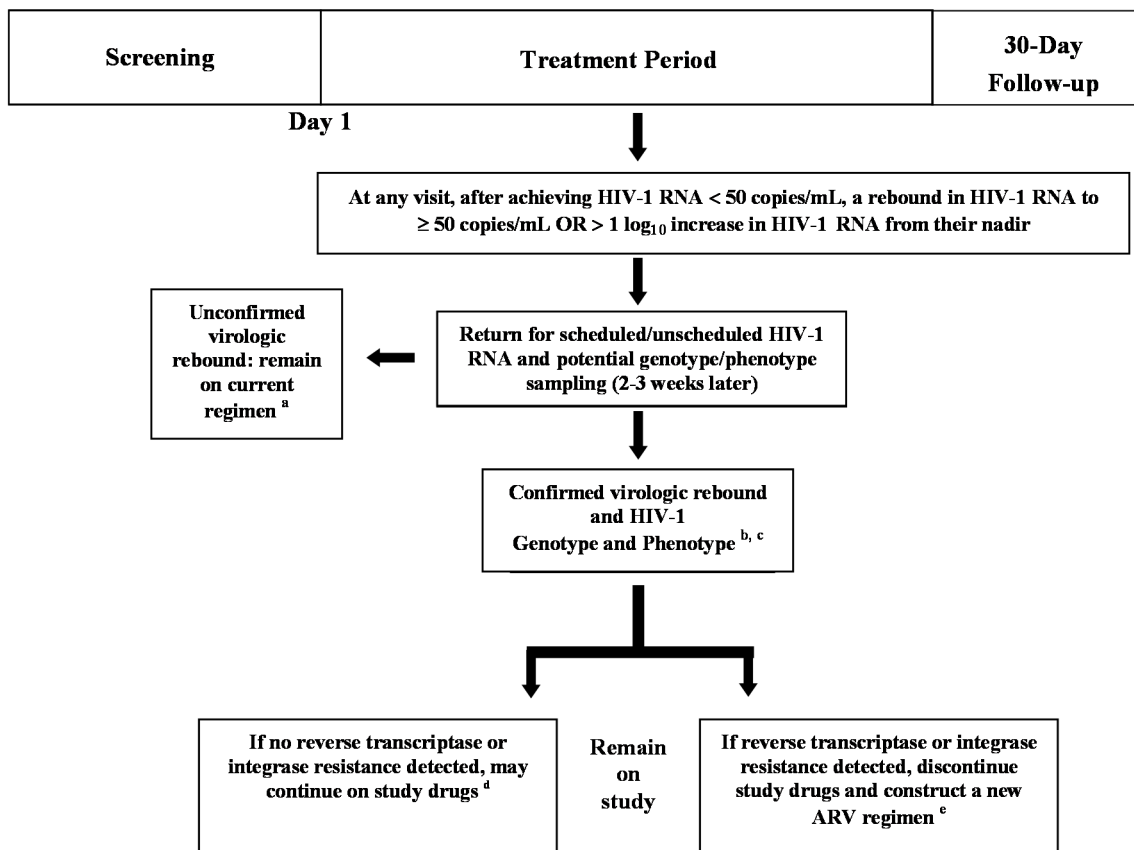
If no resistance is detected from the genotype or phenotype, the subject may remain on study drugs and a repeat HIV-1 RNA should be repeated (2 to 3 weeks after date of test with HIV-1 RNA < 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug for each 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  $\geq 200$  copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase) will be analyzed.
- c Based on the results of the genotypic and phenotypic assays, the subject will remain on study drugs or study drugs will be discontinued. If genotyping or phenotyping assay fails, a new ARV regimen may be configured at the discretion of the Investigator.
- d If no resistance is detected, HIV-1 RNA will be repeated (2-3 weeks later). Investigator reviews study drug continuation/discontinuation options and discusses with the Medical Monitor prior to study drug discontinuation
- e A new ARV regimen will be configured, at the Investigator's discretion, and the subject will remain in the study.

**6.12.2. Subjects with HIV-1 RNA  $\geq 50$  copies/mL at Study Discontinuation, Week 48, 96, 144, Week 48 OL or Week 96 OL**

Subjects with HIV-1 RNA  $\geq 50$  copies/mL at study discontinuation or last visit will be considered virologic failures. Subjects with HIV-1 RNA  $\geq 50$  copies/mL at Week 48, Week 96, Week 144, Week 48 OL or Week 96 OL will be asked to return for an unscheduled visit within the visit window for a retest.

Subjects with HIV-1 RNA  $\geq 200$  copies/mL at study drug discontinuation, last visit, Week 48, Week 96, Week 144, Week 48 OL or Week 96 OL 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 reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

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

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

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

## **7.2. Assessment of Adverse Events and Serious Adverse Events**

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

### **7.2.1. Assessment of Causality for Study Drugs and Procedures**

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

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



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

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

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

### **7.2.2. Assessment of Severity**

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

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

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

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

Requirements for collection prior to study drug initiation:

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

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

#### **7.3.1. Adverse Events**

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

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



- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

#### **7.4. Gilead Reporting Requirements**

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

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure, EU Summary of Product Characteristics (SmPC), or relevant local label as applicable.

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

#### **7.5. Toxicity Management**

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

- Clinical events and clinically significant laboratory abnormalities will be graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities ([Appendix 5](#)).
- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice

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

##### **7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event**

Continue study drug at the discretion of the Investigator.

### **7.5.2. Grade 3 Laboratory Abnormality or Clinical Event**

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product will be withheld until the toxicity returns to Grade 2. When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose upon discussion with the Gilead Sciences Medical Monitor.
- If a laboratory abnormality recurs to  $\geq$  Grade 3 following rechallenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product will be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation but requires discussion with the Gilead Sciences Medical Monitor.

### **7.5.3. Grade 4 Laboratory Abnormality or Clinical Event**

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product will be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.
- Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 CK after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product requires discussion with the Gilead Sciences Medical Monitor.

### **7.5.4. On-Treatment ALT Flare and Post-Treatment Exacerbation of Hepatitis B Management**

In On-Treatment ALT Flare is defined as:

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

#### 7.5.4.1. Management of ALT Flare in Subjects Receiving Study Medication

If laboratory results indicate elevation of ALT  $> 2 \times$  Day 1 value and  $> 10 \times$  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 (i.e.,  $> 2 \times$  Day 1 and  $> 10 \times$  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 (i.e.,  $> 2 \times$  Day 1 and  $> 10 \times$  ULN), and total bilirubin is confirmed to be  $2 \times$  Day 1 value, and INR is 0.5 above Day 1, provided both are  $> 1.5 \times$  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.

#### 7.5.4.2. Management of Exacerbation of Hepatitis B in Subjects who have Discontinued Study Medication

If laboratory results indicate (1) an ALT elevation  $> 2 \times$  Day 1 and  $> 10 \times$  ULN alone OR associated with (2) abnormal laboratory parameters suggestive of worsening hepatic function (total bilirubin  $2 \times$  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.

#### 7.5.5. Management of Potential Hepatobiliary Toxicity

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

#### 7.5.6. On-Treatment Hepatitis C Management

If a subject tests positive for HCV RNA at screening or develops signs or symptoms of active Hepatitis C virus Gilead recommends that local medical practice is followed at the discretion of the Investigator. Investigational medicinal product may be continued without dose interruption. Should the Investigator decide to initiate Hepatitis C treatment the Investigator must contact the Gilead Medical Monitor to confirm that no drug-drug interactions are expected. Subjects should return to the clinic for scheduled or unscheduled follow up visit(s) according to local medical practice for laboratory evaluations. If Hepatitis C treatment is initiated, Investigators should use the Gilead provided retest laboratory kits to manage the active Hepatitis C.

## **7.6. Special Situations Reports**

### **7.6.1. Definitions of Special Situations**

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, reports of adverse reactions in infants following exposure from breastfeeding, occupational exposure with an adverse event, and pregnancy reports regardless of an associated AE.

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

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

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

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

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

### **7.6.2. Instructions for Reporting Special Situations**

#### **7.6.2.1. Instructions for Reporting Pregnancies**

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

The subject's treatment assignment will be unblinded by the Investigator as described in Protocol Section 5.1.1.

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

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

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. Any complications during pregnancy and the outcome should be reported to Gilead PVE 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 PVE. Gilead PVE contact information is as follows:

Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

Refer to [Appendix 7](#) for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

#### 7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE 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 7.6.2.1 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 a FDC of GS-9883/F/TAF versus DTG + F/TAF in HIV-1 infected, antiretroviral treatment naïve-adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

- The secondary objectives of this study are to evaluate the efficacy, safety and tolerability of the two treatment groups through Weeks 48, 96, and 144.
- To evaluate the long term efficacy and safety of FDC GS-9883/F/TAF through OL Weeks 48 and 96.

#### **8.1.2. Primary Endpoint**

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

#### **8.1.3. Secondary Endpoint**

The secondary endpoints include:

- The proportion of subjects who achieve HIV-1 RNA < 50 copies/mL at Weeks 96 and 144 as defined by the US FDA-defined snapshot algorithm
- The proportion of subjects who achieve HIV-1 RNA < 20 copies/mL at Weeks 48, 96 and 144 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in log<sub>10</sub> HIV-1 RNA and CD4+ cell count at Weeks 48, 96, and 144
- The proportion of subjects who achieve HIV-1 RNA < 50 copies/mL at Weeks 48 OL and 96 OL as defined by Missing = Excluded and Missing = Failure algorithm
- The change from baseline in CD4+ cell count at Weeks 48 OL and 96 OL.

### **8.2. Analysis Conventions**

#### **8.2.1. Analysis Sets**

##### **8.2.1.1. All Randomized**

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

## 8.2.1.2. Efficacy

### 8.2.1.2.1. Full Analysis Set (FAS)

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

### 8.2.1.2.2. Per-Protocol (PP) Analysis Set

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

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

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

## 8.2.1.3. Safety

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

#### 8.2.1.4. Pharmacokinetics

##### 8.2.1.4.1. Pharmacokinetic (PK) Substudy Analysis Set

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

##### 8.2.1.4.2. Pharmacokinetic (PK) Analysis Set

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

##### 8.2.1.5. All GS-9883/F/TAF Analysis Set

All GS-9883/F/TAF analysis set will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of the blinded GS-9883/F/TAF or OL GS-9883/F/TAF. Subjects will be grouped into two groups: (1) All GS-9883/F/TAF group, including all subjects who randomized into GS-9883/F/TAF and received at least 1 dose of GS-9883/F/TAF; (2) DTG + F/TAF to GS-9883/F/TAF group, including all subjects who randomized to DTG + FTAF in the double-blinded phase and received at least 1 dose of OL GS-9883/F/TAF in the extension phase. This is the primary analysis set for the all GS-9883/F/TAF efficacy and safety analyses.

### 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. Logarithm (base 10) transformation will be applied to HIV-1 RNA levels for efficacy analysis.

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

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

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

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

#### **8.4. Demographic Data and Baseline Characteristics**

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

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

Baseline characteristics will include body weight, height, body mass index, eGFR, HIV-1 infection, and enrollment distribution by randomization stratum 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**

###### **8.5.1.1. Primary Efficacy Endpoint**

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

###### **8.5.1.2. US FDA-defined Snapshot Algorithm**

The analysis window at Week 48 is defined as from Study Day 295 to Study Day 378. 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 HIV-1 RNA < 50 copies/mL in the Week 48 analysis window while on randomized treatment
- **HIV-1 RNA ≥ 50 copies/mL:** this includes subjects
  - a) Who have the last available HIV-1 RNA ≥ 50 copies/mL in the Week 48 analysis window while on randomized treatment, or
  - b) Who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window and
    - i) Who discontinue study drug prior to or in the Week 48 analysis window due to lack of efficacy, or
    - ii) Who discontinue study drug prior to or in the Week 48 analysis window due to reasons other than adverse event (AE), death, or lack of efficacy and have the last available HIV-1 RNA up to 1 day after the premature discontinuation of the study drug ≥ 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 AE or death (regardless of whether the last available HIV-1 RNA up to 1 day after the premature discontinuation of the study drug < 50 copies/mL or not) or,
  - b) Discontinuation of study drug prior to or in the Week 48 analysis window due to reasons other than AE, death, or lack of efficacy (eg, withdrew consent and loss to follow-up) and the last available HIV-1 RNA up to 1 day after the premature discontinuation of the study drug < 50 copies/mL or,
  - c) Missing data during the window but on study drug.

#### 8.5.1.3. Analysis of Primary Efficacy Endpoint

The null hypothesis is that the proportion of subjects achieving HIV-1 RNA < 50 copies/mL (as defined by the US FDA-defined snapshot algorithm) at Week 48 in GS-9883/F/TAF is at least 12% lower than the response rate in DTG + F/TAF; the alternative hypothesis is that the response rate in GS-9883/F/TAF is less than 12% lower than that in DTG + F/TAF.

Non-inferiority will be assessed using the conventional confidence interval approach. The point estimate of treatment difference (GS-9883/F/TAF group – DTG + F/TAF group) and the associated 2-sided 95% confidence interval will be constructed using a normal approximation method based on stratum-stratified Mantel-Haenszel proportions, where stratification factors include baseline HIV-1 RNA level ( $\leq 100,000$  copies/mL, vs.  $> 100,000$  copies/mL) and region (US vs. Ex-US). Note that to avoid small or missing cells in analysis strata, CD4+ cell count is not stratified in the analysis because HIV-1 RNA and CD4+ cell count are highly correlated.

If non-inferiority of GS-9883/F/TAF to DTG + F/TAF is established, the lower bound of the 95% CI will be compared to 0; if the lower bound of the 95% CI is greater than 0, then superiority of GS-9883/F/TAF over DTG + F/TAF will be established.

#### 8.5.2. Secondary Analyses

The proportion of subjects who achieve HIV-1 RNA < 50 copies/mL at Weeks 96 and 144 and the proportion of subjects who achieve HIV-1 RNA < 20 copies/mL at Weeks 48, 96 and 144, as defined by the US FDA-defined snapshot algorithm, will be analyzed using the same method as for the primary efficacy endpoint.

The changes from baseline in log<sub>10</sub> HIV-1 RNA and CD4+ cell count at Weeks 48, 96, and 144 will be summarized by treatment using descriptive statistics. The differences in changes from baseline in log<sub>10</sub> HIV-1 RNA and CD4+ cell count between 2 treatments groups and the associated 95% confidence intervals will be constructed using ANOVA models, including treatment (GS-9883/F/TAF vs. DTG + F/TAF), baseline HIV-1 RNA level ( $\leq 100,000$  copies/mL vs.  $> 100,000$  copies/mL), and region (US vs. Ex-US) as fixed effects in the model.

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

### **8.5.3. Efficacy Analyses for All GS-9883/F/TAF Analysis**

The following analyses will be conducted for all GS-9883/F/TAF analysis using all GS-9883/F/TAF analysis set: (1) the proportion of subjects with HIV-1 RNA  $< 50$  copies/mL by Missing = Excluded and Missing = Failure approaches by visit, (2) the change from baseline in CD4+ Cell Count by visits, and (3) the change from baseline in CD4 % by visits. No statistical comparison will be conducted for all GS-9883/F/TAF analysis.

### **8.6. Safety Analysis**

All safety analyses will be performed using the safety analysis set for the double-blinded phase analysis and using all GS-9883/F/TAF analysis set for the all GS-9883/F/TAF analysis, unless specified otherwise.

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

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

#### **8.6.1. Extent of Exposure**

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

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

Dosing information for individual subjects will be listed.

### **8.6.2. Adverse Events**

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

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

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

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

A listing of Stage 3 Opportunistic Illnesses in HIV, can be found in [Appendix 6](#).

### **8.6.3. Laboratory Evaluations**

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

Graded laboratory abnormalities will be defined using the grading scheme defined in Grading of laboratory abnormalities attached in [Appendix 5](#).

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by treatment. If baseline data are missing, then any graded abnormality (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 intensive PK substudy, plasma concentrations of GS-9883 may be summarized by nominal sampling time using descriptive statistics. Pharmacokinetic parameters ( $C_{max}$ ,  $T_{max}$ ,  $C_{tau}$ ,  $AUC_{tau}$ , and  $T_{1/2}$ , as appropriate) will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation %, SD, median, Q1, Q3, minimum, and maximum). Plasma concentrations over time will be plotted in semi-logarithmic and linear formats as mean  $\pm$  standard deviation, and median (Q1, Q3).

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

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

## **8.8. Patient Reported Outcomes (PRO)**

The PRO measures based on questionnaires (e.g. SF-36 and HIV Symptoms Distress Module) may be summarized using descriptive statistics.

## **8.9. Sample Size**

A total of approximately 600 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 treatment groups (300 subjects per treatment group), achieves at least 95% power to detect a non-inferiority margin of 12% in Week 48 response rate (HIV-1 RNA < 50 copies/mL as defined by the US FDA-defined snapshot algorithm) difference between the 2 treatment groups. For the sample size and power computations, it is assumed that both treatment groups have a response rate of 91% (based on Gilead Studies GS-US-292-0104 and GS-US-292-0111), that the non-inferiority margin is 12%, and that the significance level of the test is at a one-sided 0.025 level. Sample size and power calculations were made using the statistical software package nQuery Advisor (Version 6.0).

## **8.10. Data Monitoring Committee**

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



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

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

#### **8.11. Analysis Schedule**

The Week 48 OL analyses will be conducted after all subjects either complete their Week 48 OL visits or prematurely discontinue from the study drug. Final analysis and/or Week 96 OL analyses will be performed after all subjects complete the study or prematurely discontinue from the study.

## **9. RESPONSIBILITIES**

### **9.1. Investigator Responsibilities**

#### **9.1.1. Good Clinical Practice**

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

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

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

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

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

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

#### **9.1.3. Informed Consent**

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

investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

#### **9.1.4. Confidentiality**

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

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

#### **9.1.5. Study Files and Retention of Records**

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

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

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

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

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

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

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

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

#### **9.1.6. Case Report Forms**

For each subject consented, an eCRF 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 or IECs, or to regulatory authority or health authority inspectors.

### **9.1.9. Protocol Compliance**

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

## **9.2. Sponsor Responsibilities**

### **9.2.1. Protocol Modifications**

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

### **9.2.2. Study Report and Publications**

A clinical study report (CSR) will be prepared and provided to the regulatory agency. 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
- Appendix 2. Study Procedures Table (Blinded Phase)
- Appendix 3. Study Procedures Table (Open Label Rollover Extension)
- Appendix 4. Management of Clinical and Laboratory Adverse Events
- Appendix 5. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities
- Appendix 6. Definitions of Stage 3 Opportunistic Illnesses in HIV (CDC Guidelines)
- Appendix 7. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

**Appendix 1. Investigator Signature Page**

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

**STUDY ACKNOWLEDGEMENT**

**A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of  
GS-9883/Emtricitabine/Tenofovir Alafenamide Versus  
Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral  
Treatment-Naïve Adults**

**GS-US-380-1490 Amendment 3, 06 May 2019**

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

**PPD**  
PPD (Printed)

**PPD**  
Signature

**06 May 2019**

Date

**INVESTIGATOR STATEMENT**

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

**Appendix 2. Study Procedures Table (Blinded Phase)**

Study Procedures	Screening <sup>a</sup>	Day 1 <sup>b</sup>	4	8	12	24	36	End of Weeks, <sup>q</sup>									Post-Week 144 <sup>e,r</sup>	End of Blinded Treatment Visit <sup>y</sup>	30-Day Follow-up <sup>p</sup>	Early Study Drugs DCc	
								48	60	72	84	96	108	120	132	144					
								Every 12 Weeks													
Informed Consent	X																				
Medical History	X																				
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X <sup>f</sup>	
Complete/Symptom-Directed Physical Exam	X	X	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X	X <sup>d</sup>	X	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X	X <sup>d</sup>	X	X <sup>d,f</sup>	X <sup>f</sup>	
12-Lead ECG (performed supine)	X	X				X		X				X				X	X <sup>w</sup>	X		X	
Questionnaires		X	X		X			X													
Height	X																				
Vital signs (blood pressure, pulse, respiration rate, and temperature), including Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X <sup>f</sup>
Urine Pregnancy Test <sup>e</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test	X																				
Chemistry Profile <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X <sup>f</sup>
Metabolic Assessments <sup>i</sup>		X			X	X		X		X		X		X		X	X <sup>s</sup>	X			
Estimated Glomerular Filtration Rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X
Hematology Profile <sup>j</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X <sup>f</sup>
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma & Urine Storage Sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
HCV Serology <sup>u</sup>	X							X				X				X	X				
HIV-1 Genotype <sup>k</sup>	X																				
HIV-1 Genotype/Phenotype <sup>e</sup>																					X <sup>e</sup>

Study Procedures	Screening <sup>a</sup>	Day 1 <sup>b</sup>	4	8	12	24	36	End of Weeks, <sup>q</sup>								Post-Week 144 <sup>e,r</sup>	End of Blinded Treatment Visit <sup>y</sup>	30-Day Follow-up <sup>p</sup>	Early Study Drugs DCc	
								48	60	72	84	96	108	120	132					144
Single PK Sample <sup>l</sup>				X		X	X													
Trough and Post Dose PK Sample <sup>m</sup>			X		X															
CCI																				
Randomization <sup>v</sup>		X																		
Provide subject dosing diary to subjects		X	X	X	X	X														
CCI																				
HBV blood panel <sup>l</sup>	X				X <sup>t</sup>	X <sup>t</sup>		X <sup>t</sup>		X <sup>t</sup>		X <sup>t</sup>		X <sup>t</sup>		X <sup>t</sup>	X			
Plasma HBV DNA <sup>l</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Study Drug Dispensation		X <sup>b</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>s</sup>		
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

- a. Evaluations to be completed within 30 days prior to Day 1.
- b. Initiation of the first dose of study drug is to take place in-clinic following completion of study procedures at the Day 1 visit.
- c. Early Study Drugs Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Visit even if the subject discontinues study drug.
- d. Symptom-directed physical examination as needed.
- e. HIV-1 genotype and phenotype testing for subjects with virologic failure. Following virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Section 6.12).
- f. Any adverse event or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.
- g. Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
- h. Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 x ULN). At Day 1, Weeks 12, 24, 48, 72, 96, 120 and 144, every 24 weeks post Week 144, and End of Blinded Treatment Visit, analyses of glucose will be done as part of the fasting metabolic assessments every 24 weeks and not as part of the chemistry profile. Additionally: TSH will be analyzed at Screening, Day 1, Weeks 24, 48, 72, 96, 120, and 144 followed by every 24 weeks post Week 144, End of Blinded Treatment Visit and Early Study Drugs Discontinuation visit. PT/INR to be performed at Day 1.

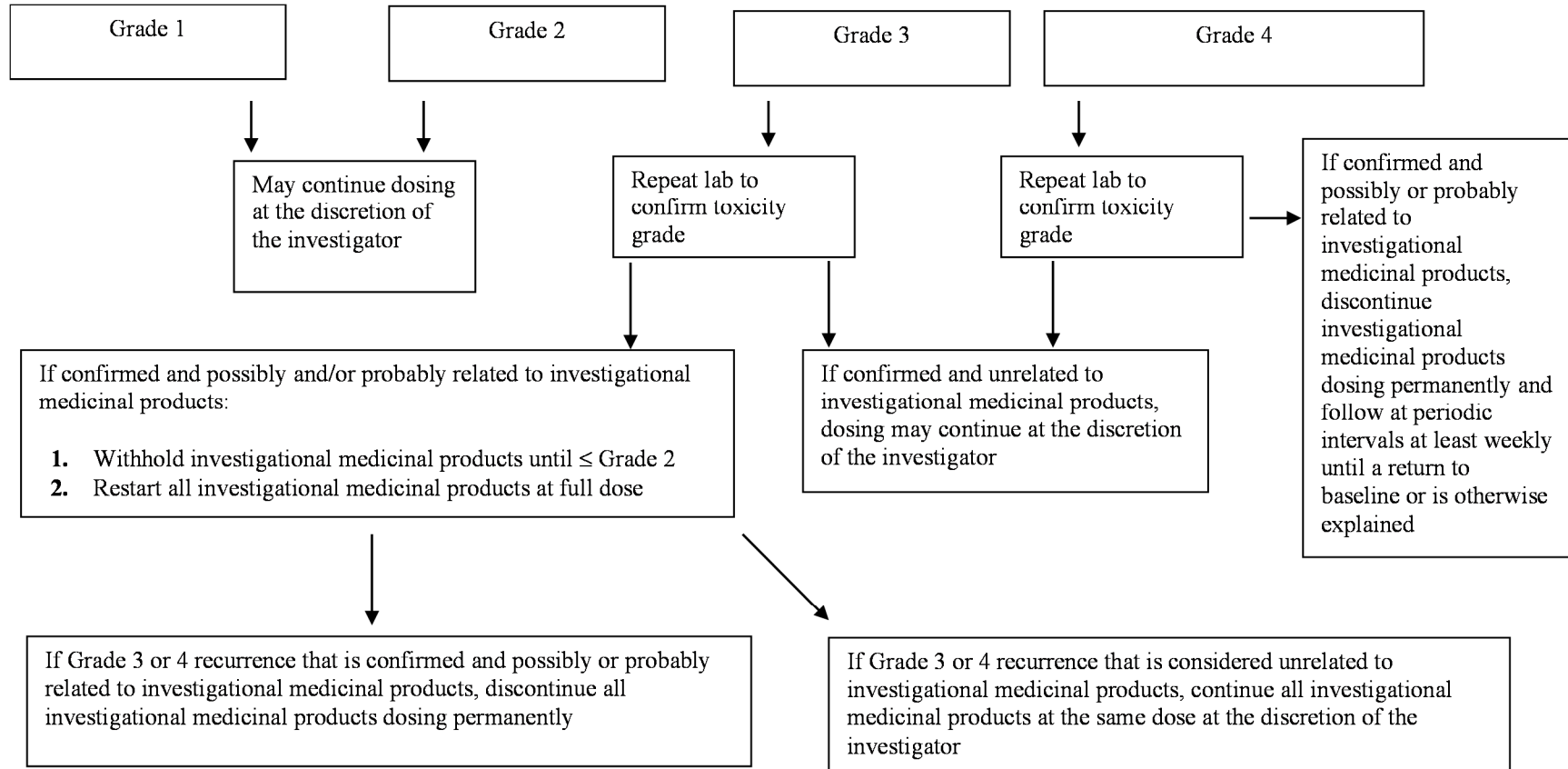


**Appendix 3. Study Procedures Table (Open Label Rollover Extension)**

Study Procedures	End of Blinded Treatment Visit <sup>a</sup>	End of Week <sup>e, l, o</sup>								30-Day Follow-up <sup>k</sup>	Early Study Drugs DC <sup>c</sup>
		12 OL	24 OL	36 OL	48 OL	60 OL	72 OL	84 OL	96 OL		
Adverse Events	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X <sup>f</sup>
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
<b>Complete</b> /Symptom-Directed Physical Exam	<b>X</b>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	<b>X</b>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	<b>X</b>	X <sup>d,f</sup>	<b>X<sup>f</sup></b>
12-Lead ECG (performed supine)	X				X				X		
Vital signs (blood pressure, pulse, respiration rate, and temperature), including Weight	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X <sup>f</sup>
Urine Pregnancy Test <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X
Chemistry Profile <sup>h</sup>	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X <sup>f</sup>
Metabolic Assessments <sup>i</sup>	X		X		X		X		X		
Estimated Glomerular Filtration Rate	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X
Hematology Profile <sup>j</sup>	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X <sup>f</sup>
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X
Plasma & Urine Storage Sample	X	X	X	X	X	X	X	X	X		X
HBV Blood Panel <sup>m</sup>			X <sup>m</sup>		X <sup>m</sup>		X <sup>m</sup>		X <sup>m</sup>		
Plasma HBV DNA <sup>m</sup>		X <sup>m</sup>	X <sup>m</sup>	X <sup>m</sup>	X <sup>m</sup>	X <sup>m</sup>	X <sup>m</sup>	X <sup>m</sup>	X <sup>m</sup>		
HCV Serology <sup>n</sup>					X <sup>n</sup>				X <sup>n</sup>		
HIV-1 Genotype/Phenotype <sup>e</sup>											X <sup>e</sup>
Study Drug Dispensation <sup>b</sup>	X <sup>b</sup>	X	X	X	X	X	X	X			
Study Drug Accountability	X	X	X	X	X	X	X	X	X		X

- a. Once the last subject completes the Week 144 visit and Gilead completes the Week 144 analysis, all subjects will return to the clinic (within 30 days  $\pm$  6 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, subjects will be given GS-9883/F/TAF FDC in an open label (OL) extension phase for 96 weeks (Week 96 OL). After Week 96 OL, subjects will discontinue the study drug, transition onto commercially available treatment and complete a 30-Day Follow-up Visit. In a country where GS-9883/F/TAF is not available, subjects will be given the option to continue OL GS-9883/F/TAF 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.
- b. Open label study drug, GS-9883/F/TAF FDC will be dispensed to subjects participating in the Open-Label Rollover extension for 96 weeks.
- c. Subjects who discontinue study drug during the open label rollover extension portion of the study will be asked to return to the clinic within 72 hours of stopping study drugs for the Early Study Drugs Discontinuation Visit followed by a 30-Day Follow-Up Visit. The subject will not continue attending the scheduled study visits.
- d. Symptom-directed physical examination as needed.
- e. HIV-1 genotype and phenotype testing for subjects with virologic failure. Following virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease, and integrase genotype and phenotype) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Section 6.12.1).
- f. Any adverse event or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to Day 1, or is otherwise explained.
- g. Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
- h. Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid and amylase (reflex lipase testing is performed in subjects with total amylase  $> 1.5 \times$  ULN). At Weeks 24 OL, 48 OL, 72 OL, 96 OL, and End of Blinded Treatment Visit, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. For all subjects, TSH will be done at the End of Blinded Treatment Visit, Weeks 24 OL, 48 OL, 72 OL, 96 OL, and Early Study Drug Discontinuation Visit.
- i. Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides) every 24 weeks. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
- j. CBC with differential and platelet count.
- k. Subjects who complete the open-label rollover extension will be required to return to the clinic 30 days after the completion of study drugs for the 30-Day Follow-Up Visit. Subjects who permanently discontinue study drugs during the open-label rollover extension will be asked to return to the clinic 30 days after the completion of the Early Study Drugs Discontinuation Visit for the 30-Day Follow-Up Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a  $\pm$  6 days window may be used.
- l. Study visits are to be completed within  $\pm$  2 days of the protocol-specified visit date based on the End of Blinded Treatment Visit date through Week 12 OL and completed within  $\pm$  6 days of the protocol-specified visit date every 12 weeks thereafter, unless otherwise specified
- m. **For subjects who meet the definition of HBV infection at any visit:** The following will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative) and HBeAg (if negative, reflex HBeAb) (every 24 weeks) and Plasma HBV DNA (every 12 weeks).  
**For subjects who do NOT meet the definition of HBV infection at any visit:** The following will be conducted by the central laboratory: Hepatitis B surface antibody (HBsAb), Hepatitis B virus core antibody (HBcAb), and Hepatitis B virus surface antigen serology (HBsAg). Subjects who are HBsAg and/or HBcAb positive will have a reflex test for HBV DNA (viral load) (Weeks 48 OL and 96 OL)
- n. Hepatitis C virus (HCVAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed. (Weeks 48 OL and 96 OL)
- o. After Week 96 OL, if subject is in a country where GS-9883/F/TAF is not available, the study procedures completed by the subject will be the same at every 48 weeks (i.e. OL Weeks 48, 96) and at every 12 weeks (i.e. OL Weeks 12, 24, 36, 60, 72, 84) 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.

#### Appendix 4. Management of Clinical and Laboratory Adverse Events





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

Antiviral Toxicity Grading Scale Version: 01 April 2015

<b>HEMATOLOGY</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
Hemoglobin HIV POSITIVE <b>Adult and Pediatric ≥ 57 Days</b>	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 <b>Adult and Pediatric ≥ 57 Days</b>	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
<b>Infant, 36–56 Days</b> (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
<b>Infant, 22–35 Days</b> (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
<b>Infant, 1–21 Days</b> (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) <b>Adult and Pediatric, 7 Months#</b>	1000 to 1300/mm <sup>3</sup> 1.00 to 1.30 GI/L	750 to < 1000/mm <sup>3</sup> 0.75 to < 1.00 GI/L	500 to < 750/mm <sup>3</sup> 0.50 to < 0.75 GI/L	< 500/mm <sup>3</sup> < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY <b>Adult and Pediatric &gt; 13 Years</b>	300 to 400/mm <sup>3</sup> 300 to 400/μL	200 to < 300/mm <sup>3</sup> 200 to < 300/μL	100 to < 200/mm <sup>3</sup> 100 to < 200/μL	< 100/mm <sup>3</sup> < 100/μL

<b>HEMATOLOGY</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
Absolute Lymphocyte Count HIV NEGATIVE ONLY <b>Adult and Pediatric</b> <b>&gt; 13 Years</b>	600 to 650/mm <sup>3</sup> 0.60 to 0.65 GI/L	500 to < 600/mm <sup>3</sup> 0.50 to < 0.60 GI/L	350 to < 500/mm <sup>3</sup> 0.35 to < 0.50 GI/L	< 350/mm <sup>3</sup> < 0.35 GI/L
Platelets	100,000 to < 125,000/mm <sup>3</sup> 100 to < 125 GI/L	50,000 to < 100,000/mm <sup>3</sup> 50 to < 100 GI/L	25,000 to < 50,000/mm <sup>3</sup> 25 to < 50 GI/L	< 25,000/mm <sup>3</sup> < 25 GI/L
WBCs	2000/mm <sup>3</sup> to 2500/mm <sup>3</sup> 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm <sup>3</sup> 1.50 to < 2.00 GI/L	1000 to < 1,500/mm <sup>3</sup> 1.00 to < 1.50 GI/L	< 1000/mm <sup>3</sup> < 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.

<b>CHEMISTRY</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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 <b>Adult and Pediatric ≥ 1 Year</b>	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
<b>Infant &lt;1 Year</b>	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	2.0 to < 2.5 mEq/L 2.0 to <2.5 mmol/L	< 2.0 mEq/L <2.0 mmol/L
Hyperkalemia <b>Adult and Pediatric ≥ 1 Year</b>	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
<b>Infant &lt;1 Year</b>	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia <b>Adult and Pediatric ≥ 1 Month</b>	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
<b>Infant, &lt; 1 Month</b>	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

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

CHEMISTRY				
	Grade 1	Grade 2	Grade 3	Grade 4
<b>Hypophosphatemia</b> <b>Adult and Pediatric</b> <b>&gt; 14 Years</b>  <b>Pediatric 1 Year–14 Years</b>  <b>Pediatric &lt; 1 Year</b>	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
	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
	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
<b>Hyperbilirubinemia</b> <b>Adult and Pediatric</b> <b>&gt; 14 Days</b>  <b>Infant, ≤ 14 Days</b> (non-hemolytic)  <b>Infant, ≤ 14 Days</b> (hemolytic)	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
	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
	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
<b>Hypouricemia</b> <b>Adult and Pediatric</b> <b>1 year</b>  <b>Infant &lt; 1 Year</b>	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
	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

<b>CHEMISTRY</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Bicarbonate Adult and Pediatric 4 Years</b>	16.0 mEq/L to < LLN	11.0 to < 16.0 mEq/L	8.0 to < 11.0 mEq/L	< 8.0 mEq/L
	16.0 mmol/L to < LLN	11.0 to < 16.0 mmol/L	8.0 to < 11.0 mmol/L	< 8.0 mmol/L
<b>Pediatric &lt; 4 Years</b>	NA	11.0 mEq/L to < LLN	8.0 to < 11.0 mEq/L	< 8.0 mEq/L
		11.0 mmol/L to < LLN	8.0 to < 11.0 mmol/L	< 8.0 mmol/L
<b>Triglycerides (Fasting)</b>	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
<b>LDL (Fasting) Adult</b>	130 to 160 mg/dL	>160 to 190 mg/dL	> 190 mg/dL	NA
	3.35 to 4.15 mmol/L	>4.15 to 4.92 mmol/L	>4.92 mmol/L	
<b>LDL (Fasting) Pediatric &gt;2 to &lt;18 years</b>	110 to 130 mg/dL	>130 to 190 mg/dL	> 190 mg/dL	NA
	2.84 to 3.37 mmol/L	>3.37 to 4.92 mmol/L	>4.92 mmol/L	
<b>Hypercholesterolemia (Fasting)</b>	200 to 239 mg/dL	> 239 to 300 mg/dL	> 300 mg/dL	NA
	5.16 to 6.19 mmol/L	> 6.19 to 7.77 mmol/L	> 7.77 mmol/L	
<b>Pediatric &lt; 18 Years</b>	170 to 199 mg/dL	> 199 to 300 mg/dL	> 300 mg/dL	NA
	4.39 to 5.15 mmol/L	> 5.15 to 7.77 mmol/L	> 7.77 mmol/L	
<b>Creatine Kinase</b>	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.

<b>ENZYMES</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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 <b>Pediatrics &lt;16 years</b>	-	2.0 to < LLN g/dL 20 to < LLN g/L	< 2.0 g/dL < 20 g/L	NA
<b>16 years</b>	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

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



<b>CARDIOVASCULAR</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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
<b>Pediatric ≤ 17 Years</b> (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

<b>CARDIOVASCULAR</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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
<b>Pediatric ≤ 16 Years</b>	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
<b>Pediatric ≤ 16 Years</b>	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

<b>RESPIRATORY</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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
<b>Pediatric &lt; 14 Years</b>	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

<b>OCULAR/VISUAL</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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)

<b>SKIN</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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

<b>GASTROINTESTINAL</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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 <b>Adult and Pediatric ≥ 1 Year</b>  <b>Pediatric &lt; 1 Year</b>	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr  Liquid stools (more unformed than usual) but usual number of stools	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.  Liquid stools with increased number of stools OR Mild dehydration	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated  Liquid stools with moderate dehydration	Life-threatening consequences (eg, hypotensive shock)  Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

<b>GASTROINTESTINAL</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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)

<b>NEUROLOGICAL</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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

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



<b>NEUROLOGICAL</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure – <b>Pediatric &lt; 18 Years</b>	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

<b>MUSCULOSKELETAL</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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  <b>Pediatric &lt; 21 Years</b>	BMD t-score or z-score -2.5 to -1.0  BMD z-score -2.5 to -1.0	BMD t-score or z-score < -2.5  BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)  Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences  Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

<b>SYSTEMIC</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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  <b>Pediatric ≤ 15 Years</b>	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm <sup>2</sup> )  <b>Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter</b>	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm <sup>2</sup> )  <b>Erythema OR Induration OR Edema &gt; 2.5 cm diameter but &lt; 50% surface area of the extremity segment (eg, upper arm/thigh)</b>	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage  <b>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</b>	Necrosis (involving dermis and deeper tissue)  <b>Necrosis (involving dermis and deeper tissue)</b>
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

<b>ENDOCRINE/METABOLIC</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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

<b>GENITOURINARY</b>				
	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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

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

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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

- 1) Candidiasis of bronchi, trachea, or lungs
- 2) Candidiasis of esophagus
- 3) Cervical cancer, invasive
- 4) Coccidioidomycosis, disseminated or extrapulmonary
- 5) Cryptococcosis, extrapulmonary
- 6) Cryptosporidiosis, chronic intestinal (> 1 month duration)
- 7) Cytomegalovirus disease (other than liver, spleen or nodes)
- 8) Cytomegalovirus retinitis (with loss of vision)
- 9) Encephalopathy, HIV-related
- 10) Herpes simplex: chronic ulcer(s) (> 1 month duration); or bronchitis, pneumonitis or esophagitis
- 11) Histoplasmosis, disseminated or extrapulmonary
- 12) Isosporiasis, chronic intestinal (> 1 month duration)
- 13) Kaposi's sarcoma
- 14) Lymphoma, Burkitt's (or equivalent term)
- 15) Lymphoma, immunoblastic (or equivalent term)
- 16) Lymphoma, primary, of brain
- 17) *Mycobacterium avium* complex or *Mycobacterium 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 2008](#)}



## **Appendix 7. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements**

### **1) Definitions**

#### **a. Definition of Childbearing Potential**

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

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

#### **b. Definition of Male Fertility**

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

### **2) Contraception Requirements for Female Subjects**

#### **a. Study Drug Effects on Pregnancy and Hormonal Contraception**

The data on GS-9883/F/TAF in pregnant women is limited or not available. There is no suspicion of human teratogenicity based on class effects or genotoxic potential. Relevant non-clinical reproductive studies for human pregnancy do not indicate a strong suspicion of human teratogenicity/fetotoxicity. Data from clinical pharmacokinetic interaction studies of GS-9883 and F/TAF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception or that the effect on hormonal contraception is insignificant. Please refer to the latest version of the GS-9883/F/TAF investigator's brochure, the F/TAF investigator's brochure and the current Prescribing Information and local product labeling for DTG for additional information.

#### **b. Contraception Requirements for Female Subjects of Childbearing Potential**

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Day 1 visit prior to randomization. At minimum a pregnancy test will be performed at the end of relevant systemic exposure. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even for women of childbearing potential with infrequent or irregular periods. Female subjects must agree to one of the following from Screening until 30 days following the end of relevant systemic exposure.

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Or

- Consistent and correct use of one hormonal method and one barrier method
  - Barrier methods
    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Male condom (with or without spermicide)
  - Hormonal methods
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

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

### **3) Contraception Requirements for Male Subjects**

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

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

### **4) Unacceptable Birth Control Methods**

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

### **5) Procedures to be Followed in the Event of Pregnancy**

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section [7.3](#).