## Study Title:
A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults

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

## IND Number:
125589

## EudraCT Number:
2015-004011-20

## Clinical Trials.gov Identifier:
NCT02603107

## Indication:
HIV-1 Infection

## Protocol ID:
GS-US-380-1878

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## Protocol Version/Date:
- **Original:** 21 October 2015
- **Amendment 1:** 19 February 2016
- **Amendment 2:** 19 October 2016

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PROTOCOL SYNOPSIS

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

Study Title: A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults

IND Number: 125589
EudraCT Number: 2015-004011-20
Clinical Trials.gov Identifier: NCT02603107

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

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

- To evaluate the efficacy of switching to a fixed dose combination (FDC) of GS-9883/emtricitabine/tenofovir alafenamide (GS-9883/F/TAF) versus continuing on a regimen consisting of boosted atazanavir (ATV) or darunavir (DRV) plus either emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or abacavir/lamivudine (ABC/3TC) in HIV-1 infected adult subjects who are virologically suppressed as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48

The secondary objective of this study is as follows:

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

Study Design: Randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of switching to a FDC of GS-9883/F/TAF in HIV-1 infected subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a regimen consisting of ritonavir (RTV) or cobicistat (COBI) boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months prior to screening.
Subjects who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to one of the following two treatment groups:

**Treatment Group 1**: Switch to a FDC of GS-9883/emtricitabine/tenofovir alafenamide (GS-9883/F/TAF) administered orally, once daily without regard to food (n=260)

**Treatment Group 2**: Remain on current antiretroviral regimen consisting of ritonavir or cobicistat boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally, once daily with food (n=260)

Investigators must provide a prescription to subjects in Treatment Group 2. Subjects in Treatment Group 2 are responsible for obtaining their ARV regimen.

Randomization will be stratified by the prior treatment regimen group (i.e., TDF containing regimens [ritonavir or cobicistat boosted ATV or DRV plus FTC/TDF] and non-TDF containing regimens [ritonavir or cobicistat boosted ATV or DRV plus ABC/3TC]) at screening.

**Number of Subjects**
- Planned: Approximately 520 subjects in total.
- Approximately 260 subjects in each Treatment Group 1 and Treatment Group 2

**Target Population**: HIV-1 infected subjects ≥ 18 years old who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen containing boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months prior to screening and who are INSTI naive.

**Duration of Treatment**: Duration of this study is at least 48 weeks.

At the Week 48 Visit, subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC for an additional 96 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

Subjects who complete the study through Week 48 Visit and do not further continue participation in the study, will be required to return to the clinic 30 days after the completion of the study drugs for a 30-Day Follow-Up Visit.
Diagnosis and Main Eligibility Criteria:

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

- Currently receiving a once daily antiretroviral regimen consisting of ritonavir or cobicistat boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months preceding the screening visit.

- Currently on a stable regimen for ≥ 6 months preceding the Screening visit with documented plasma HIV-1 RNA < 50 copies/mL for ≥ 6 months preceding the Screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL).

  — Prior changes in antiretroviral regimen are only allowed due to tolerability issues or for regimen simplification.

  Unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or “blip”) prior to screening are acceptable. (If the lower limit of detection of the local HIV-1 RNA assay is < 50 copies/mL [e.g., < 20 copies/mL], the plasma HIV-1 RNA level cannot exceed 50 copies/mL on two consecutive HIV-1 RNA tests)

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

- No previous use of any approved or experimental integrase strand transfer inhibitor (INSTI)

- No documented or suspected resistance to FTC, TFV, ABC or 3TC, including but not limited to the reverse transcriptase resistance mutations K65R and M184V/I

- Estimated GFR ≥ 50 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 48 weeks. For all eligible subjects, blood will be collected at Day 1, Weeks 4, 8, 12, and then every 12 weeks through Week 48. 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.

Urine will be collected and stored for possible evaluations of renal tubular function including urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2 microglobulin.

Adverse events and concomitant medications will be assessed at each visit.
Test Product, Dose, and Mode of Administration:
FDC of GS-9883 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (GS-9883/F/TAF) administered orally, once daily without regard to food.

Reference Therapy, Dose, and Mode of Administration:
Current antiretroviral drug regimen consisting of ritonavir or cobicistat boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally, once daily with food.

Criteria for Evaluation:

Safety: Adverse events, clinical laboratory tests to evaluate the safety and tolerability of the treatment regimens.

Efficacy: The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as defined by the United States (US) Food and Drug Administration [FDA]-defined snapshot algorithm.

The secondary efficacy endpoints include:
- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count at Week 48

Pharmacokinetics: An intensive pharmacokinetic (PK) substudy will be performed at the Weeks 4 or 8 visits in a subset of Treatment Group 1 subjects (target n=24) at study sites able to conduct this testing.

For all subjects in Treatment Group 1 who are 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 in Treatment Group 1 who are 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 parameters may be summarized as applicable.
Optional Genomic Testing:

Patient Reported Outcomes:

Short Form 36 Health Survey (SF-36), HIV Symptoms Distress Module Index, Work Productivity and Activity Impairment Questionnaire (WPAI), and UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) will be administered at Day 1, Weeks 4, 12 and 48. Visual Analog Scale (VAS) Adherence Questionnaire will be administered at Day 1 and all visits up to Week 48.

Statistical Methods:

The primary analysis will consist of a non-inferiority evaluation of switching to GS-9883/F/TAF versus maintaining an antiretroviral drug regimen consisting of boosted ATV or DRV plus either FTC/TDF or ABC/3TC (i.e., boosted PI plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) [boosted PI + 2 NRTIs]) with respect to the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL as defined by the US FDA-defined snapshot algorithm at Week 48. It will be concluded that GS-9883/F/TAF is non-inferior to the boosted PI + 2 NRTIs if the upper bound of the 2-sided 95% confidence interval (CI) of the difference between treatment groups (GS-9883/F/TAF – boosted PI + 2 NRTIs) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL is less than 4% (i.e., a margin of 4% is applied to non-inferiority assessment). The 2-sided 95% CIs will be constructed based on the exact method.

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm will also be summarized. The 2-sided 95% CIs will be constructed in the same manner as described for the primary efficacy endpoint.
The change from baseline in CD4+ cell count at Week 48 will be summarized using descriptive statistics. The differences and the associated 95% CIs will be constructed using Analysis of Variance (ANOVA) model, including treatment (GS-9883/F/TAF vs. boosted PI + 2 NRTIs) as a fixed effect in the model.

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

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

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.
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<tr>
<td>°F</td>
<td>degrees Fahrenheit</td>
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<tr>
<td>ABC/3TC</td>
<td>abacavir/lamivudine, Epzicom® Kivexa®</td>
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<td>PSQI</td>
<td>Pittsburgh Sleep Quality Index</td>
</tr>
<tr>
<td>PT</td>
<td>preferred term</td>
</tr>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>QD</td>
<td>once daily</td>
</tr>
<tr>
<td>RAL</td>
<td>raltegravir</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>SA</td>
<td>single agent</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form 36 Health Survey</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TAF</td>
<td>tenofovir alafenamide</td>
</tr>
<tr>
<td>TDF</td>
<td>tenofovir disoproxil fumarate, Viread®</td>
</tr>
<tr>
<td>TFV-DP</td>
<td>tenofovir diphosphate (TFVpp)</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>the time (observed time point) of $C_{\text{max}}$</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
<tr>
<td>UCLA SCTC GIT</td>
<td>UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>uridine 5'-diphospho-glucuronyltransferase</td>
</tr>
<tr>
<td>UGT</td>
<td>uridine glucuronosyltransferase</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of the normal range</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analog scale</td>
</tr>
<tr>
<td>WPAI</td>
<td>Work Productivity and Activity Impairment Questionnaire</td>
</tr>
</tbody>
</table>
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 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.

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. 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. 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.

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-trancriptase 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 secondarily by CYP3A. GS-9883 does not inhibit major human CYP isoforms or UGT1A1 at concentrations up to 25 μM. Consequently, GS-9883 is unlikely to be a clinically relevant inhibitor of these enzymes, and is not expected to inhibit the metabolic clearance of drugs metabolized by these enzymes. GS-9883 only modestly inhibits renal transporter OCT2 (IC_{50} = 0.42 μM). As a result, GS-9883 is not expected to significantly interfere with the key transporter responsible for creatinine tubular elimination at the clinically projected C_{max}. Additionally, the risk that GS-9883 will affect the OCT2-mediated excretion of co-administered drugs is considered to be low.
GS-9883 does not activate AhR and only weakly activates PXR at concentrations up to 50 μM (less than 5% and 40% of activation, respectively, compared to positive control compound). Therefore, GS-9883 is not expected to act as an inducer through PXR- or AhR-mediated pathways at the doses and exposure levels projected in clinical use.

1.2.2.2. Toxicology

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

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

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

No GS-9883-related effects were observed in the mid-dose group (200 mg/kg/day) which was considered the no-observed-effect-level (NOEL). The estimated margin of exposure at the NOEL was approximately 5.1-fold based on expected human exposure with the once daily dosing of the GS-9883/F/TAF (50/200/25 mg) tablet.
A standard battery of in vitro and in vivo studies was performed to assess the genotoxic potential of GS-9883. There was no evidence of mutagenic or clastogenic activity in an in vitro bacterial reverse mutation assay (Study TX-141-2026), a chromosomal aberration assay in human lymphocytes (Study TX-141-2027), or in a rat micronucleus test (Study TX-141-2029).

1.2.3. Clinical Trials of GS-9883

Clinical trials entailing the use of GS-9883 include:

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

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

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

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

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

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

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

- GS-US-141-1485, a Phase 1 adaptive study to evaluate transporter, CYP-mediated and UGT1A1 drug-drug interactions between GS-9883 and probe drugs (completed)
• GS-US-141-1487, a Phase 1 randomized, Blinded, Placebo-Controlled Phase 1 Study Evaluating the Effect of GS-9883 on Renal Function as Assessed by Markers of Glomerular Filtration Rate (completed)

• GS-US-311-1790, a Phase 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-380-1999, 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 $T_{\text{max}}$ 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$_{\text{inf}}$ and $C_{\text{max}}$ (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$_{24\text{hr}}$ of 1.6.

**Table 1-1.**  

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

$T_{1/2}$ and $T_{\text{max}}$: 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 $T_{\text{max}}$ 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 $C_{\text{max}}$ 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.

<table>
<thead>
<tr>
<th>GS-9883 PK Parameter</th>
<th>Mean (%CV)</th>
<th>5 mg (N = 6)</th>
<th>25 mg (N = 6)</th>
<th>50 mg (N = 6)</th>
<th>100 mg (N = 6)</th>
<th>300 mg (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-24}$ (hr*ng/mL)</td>
<td>9033.6 (8.2)</td>
<td>27,775.1 (28.3)</td>
<td>58,371.4 (18.9)</td>
<td>79,773.8 (18.9)</td>
<td>180,714.3 (17.6)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>709.7 (9.5)</td>
<td>2220.0 (35.6)</td>
<td>4648.3 (18.7)</td>
<td>6248.3 (26.8)</td>
<td>13,716.7 (19.1)</td>
<td></td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>1.50 (1.50, 1.50)</td>
<td>1.75 (1.00, 3.00)</td>
<td>1.50 (1.00, 2.00)</td>
<td>2.50 (2.00, 3.00)</td>
<td>2.50 (2.00, 4.00)</td>
<td></td>
</tr>
<tr>
<td>$AUC_{\text{inf}}$ (hr*ng/mL)</td>
<td>14,392.0 (16.7)</td>
<td>50,008.2 (26.6)</td>
<td>89,710.1 (22.7)</td>
<td>126,785.8 (23.7)</td>
<td>277,200.2 (16.7)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>982.5 (7.9)</td>
<td>3455.0 (24.1)</td>
<td>6538.3 (17.6)</td>
<td>9396.7 (20.8)</td>
<td>19,900.0 (21.2)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{tau}}$ (ng/mL)</td>
<td>400.83 (26.9)</td>
<td>1322.00 (27.3)</td>
<td>2241.67 (28.2)</td>
<td>3145.00 (26.1)</td>
<td>6758.33 (21.6)</td>
<td></td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>1.50 (1.00, 2.00)</td>
<td>3.00 (2.00, 3.00)</td>
<td>1.75 (1.50, 2.00)</td>
<td>1.75 (1.50, 3.00)</td>
<td>4.00 (2.00, 4.00)</td>
<td></td>
</tr>
</tbody>
</table>

Accumulation Ratio of AUC (%) 160.5 (19.0) 182.2 (17.1) 154.0 (15.9) 158.5 (12.1) 157.5 (22.6)

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 $C_{\text{max}}$ and $AUC_{\text{inf}}$ 101% (90% CI of GLSM ratio 165.93% to 242.74%) and 84% (90% CI of GLSM ratio 152.05% to 222.59%), respectively. There were no apparent changes in clearance and $T_{1/2}$ following administration with food, indicating that food enhanced the bioavailability of GS-9883 by improving its solubility and/or absorption.
Table 1-3. GS-US-141-1218: Statistical Comparison of GS-9883 Pharmacokinetic Parameters Following Single-Dose Administration of GS-9883 in the Fasted and Fed States (GS-9883 PK Analysis Set)

<table>
<thead>
<tr>
<th>GS-9883 PK Parameter</th>
<th>Mean (%CV)</th>
<th>Test GS-9883 100 mg Fed (n=8)</th>
<th>Reference GS-9883 100 mg Fasted (n=8)</th>
<th>% GLSM Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt; (hr*ng/mL)</td>
<td>214,146.3 (15.9)</td>
<td>117,777.1 (23.3)</td>
<td>183.97 (152.05, 222.59)</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;last&lt;/sub&gt; (hr*ng/mL)</td>
<td>209,259.9 (15.1)</td>
<td>115,681.7 (24.0)</td>
<td>183.58 (151.91, 221.86)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>11,268.8 (15.1)</td>
<td>5885.0 (34.9)</td>
<td>200.69 (165.93, 242.74)</td>
<td></td>
</tr>
</tbody>
</table>

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\textsubscript{95} Values (GS-9883 PK Analysis Set)

<table>
<thead>
<tr>
<th>GS-9883 dose</th>
<th>n</th>
<th>Median (range) C\textsubscript{tau, SS} (ng/mL)</th>
<th>Median (range) paIQ\textsubscript{95} a</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>4</td>
<td>206.5 (146.0 to 342.0)</td>
<td>1.3 (0.9 to 2.1)</td>
</tr>
<tr>
<td>25 mg</td>
<td>4</td>
<td>797.5 (714.0 to 1900.0)</td>
<td>4.9 (4.4 to 11.7)</td>
</tr>
<tr>
<td>50 mg</td>
<td>4</td>
<td>2170.0 (852.0 to 3020.0)</td>
<td>13.4 (5.3 to 18.6)</td>
</tr>
<tr>
<td>100 mg</td>
<td>4</td>
<td>4190.0 (3730.0 to 5970.0)</td>
<td>25.9 (23.0 to 36.9)</td>
</tr>
</tbody>
</table>

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

The mean and 95% CIs of change from baseline in HIV-1 RNA (log\textsubscript{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\textsubscript{10} copies/mL) (PP Analysis Set)

Mean viral load change on Day 11 was -2.08 log\textsubscript{10} in the 25 mg cohort, -2.06 log\textsubscript{10} in the 50 mg cohort, and -2.43 log\textsubscript{10} in the 100 mg cohort. Time weighted average change from baseline at Day 11 (DAVG11) was -0.92 log\textsubscript{10} in the 5 mg cohort, -1.33 log\textsubscript{10} in the 25 mg cohort, -1.37 log\textsubscript{10} in the 50 mg cohort and -1.61 log\textsubscript{10} in the 100 mg cohort. Viral suppression (HIV-1 RNA < 50 copies/mL) was ever achieved by the end of the study (Day 17) by 1 subject (25.0%) in the GS-9883 50 mg group and 2 subjects (50%) in the GS-9883 100 mg group.
1.2.3.3. Summary of Phase 2 Study (GS-US-141-1475)

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

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

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

Week 24 interim data are summarized below.

Subject Disposition and Baseline Characteristics

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

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

Key baseline disease characteristics (ie, viral load, CD4 cell count, and eGFRCG) 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) log10 copies/mL, with 82.7% of subjects having ≤ 100,000 copies/mL at baseline; 5 subjects had > 400,000 copies/mL at baseline; 4 of these subjects were randomized to GS-9883+F/TAF and 1 subject was randomized to DTG+F/TAF.

Median (Q1, Q3) baseline CD4 cell count was 444 (316, 595) cells/μL, with 41.8% of subjects having ≥ 500 cells/μL at baseline. Median (Q1, Q3) baseline eGFRCG 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 60 copies/mL.
Following initiation of study drug, the increases from baseline in CD4 cell count were similar between treatment groups. Mean (SD) baseline CD4 cell counts were as follows: GS-9883+F/TAF 471 (190.9) cells/μL; DTG+F/TAF 507 (271.0) cells/μL; p = 0.35. The mean (SD) change in CD4 cell count from baseline to Week 12 was similar between the 2 treatment groups as follows: GS-9883+F/TAF, +170 (150.0) cells/μL; DTG+F/TAF, +173 (220.5) cells/μL (difference in least squares mean [LSM]: 0; 95% CI: −76 to 76; p = 1.00). There were similar increases in the mean (SD) CD4 cell count in both treatment groups Week 24: GS-9883+F/TAF, +189 (177.8) cells/μL; DTG+F/TAF, +157 (163.2) cells/μL (difference in LSM: 39; 95% CI: −35 to 113; p = 0.30).

Interim Virology Resistance Data

Through Week 24, no emergent drug resistance was detected.

Safety Results

Adverse Events

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

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

- **DTG+F/TAF**: nausea (12.1%, 4 subjects); diarrhea (9.1%, 3 subjects)

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

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

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

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

There were no clinically significant changes from baseline or differences between treatment groups in the median values for hematology, chemistry, or metabolic parameters. There were similar increases from baseline in median (Q1, Q3) serum creatinine in both treatment groups at Week 24: GS-9883+F/TAF 0.12 (0.06, 0.18) mg/dL; DTG+F/TAF 0.13 (0.05, 0.21) mg/dL. There were decreases in median (Q1, Q3) eGFR\text{CG} at Week 24, which were smaller in the GS-9883+F/TAF compared with the DTG+F/TAF group: GS-9883+F/TAF \text{−}13.3 (−19.9, −4.0) \text{mL/min}; DTG+F/TAF \text{−}17.2 (−25.7, −6.9) \text{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: \text{−}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: \text{−}35 to 113; p = 0.30).

- No resistance to any INSTIs, NRTIs, NNRTIs, or PIs was detected through Week 24.

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

1.3. Information about Emtricitabine (Emtriva®, FTC)

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

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

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

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

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

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

Clinical trials entailing the use of tenofovir alafenamide include:

- GS-US-120-1101, a Phase 1/2 study of the pharmacokinetics and antiviral activity of GS-7340 (50 mg and 150 mg) in HIV-infected subjects (completed)
- GS-US-120-0104, a Phase 1b study of the pharmacokinetics and antiviral activity of GS-7340 (8 mg, 25 mg, 40 mg) in HIV infected subjects (completed)
- GS-US-120-0107, a Phase 1, partially-blinded, randomized, placebo- and positive controlled study to evaluate the effect of GS-7340 on the QT/QTc interval in healthy subjects (completed)

- GS-US-120-0108, a Phase 1, open-label, parallel-design study to evaluate the pharmacokinetics of GS-7340 in subjects with severe renal impairment (completed)

- GS-US-120-0109, a Phase 1 study to evaluate the pharmacokinetics, metabolism and excretion of GS-7340 (completed)

- GS-US-120-0114, a Phase 1, open-label, parallel-group, single dose study to evaluate the pharmacokinetics of tenofovir alafenamide in subjects with normal and impaired hepatic function (completed)

- GS-US-120-0117, a Phase 1 single-dose study evaluating the pharmacokinetic drug interaction potential between rilpivirine and tenofovir alafenamide (completed)

- GS-US-120-0118, a Pharmacokinetic study evaluating the drug interaction potential of tenofovir alafenamide with a boosted protease inhibitor or unboosted integrase inhibitor in healthy subjects (completed)

- GS-US-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 AUClast of TAF when administered with a high-fat meal was 177% (90% CI: 166% to 188%), and the TAF Cmax 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 Cmax when administered with food was accompanied by a delay in Tmax (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-292-0109, a Phase 3 open-label study to evaluate switching from a TDF-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed, HIV-1 positive subjects (ongoing)
- GS-US-292-0112, a Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide single-tablet Regimen in HIV-1 positive patients with mild to moderate renal impairment (ongoing)
- GS-US-292-0117, a Phase 3, two-part study to evaluate the efficacy of Tenofovir Alafenamide versus placebo added to a failing regimen followed by treatment with Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1 positive, antiretroviral treatment-experienced adults (ongoing)
• GS-US-292-0119, a Phase 3 open-label study to evaluate switching from optimized stable antiretroviral regimens containing darunavir to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) single tablet regimen (STR) plus darunavir (DRV) in treatment experienced HIV-1 positive adults (ongoing)

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

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

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

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

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

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

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

1.5.1. GS-US-141-1233: 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$_{inf}$ and C$_{max}$ were 27% and 31% higher, respectively, following GS-9883/F/TAF (75/200/25 mg) FDC administration than following administration of single-agent GS-9883 (75 mg) with the F/TAF (200/25 mg) FDC. FTC and TAF exposure was similar following administration of GS-9883/F/TAF (75/200/25 mg) or single-agent GS-9883 (75 mg) with the F/TAF (200/25 mg) FDC.

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

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

Cohort 2 Results:

Pharmacokinetic Results

The PK results from Study GS-US-141-1233 demonstrated that the GS-9883 AUC_{inf} and C_{max} following administration of the 50mg GS-9883 FDC tablets was 79% and 78%, respectively of those observed in the same study following co-administration of GS-9883 75 mg single agent with F/TAF (200/25 mg) under fasted conditions. The GS-9883 exposures of 50 and 75 mg fixed dose combination tablets were approximately dose proportional under fasted and fed conditions and a high fat and moderate fat meal had similar impact on GS-9883 with AUC_{inf} increasing by 24%. The steady state p_{d}IQ_{5} 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. Rationale for this Study

As treatment guidelines recommend early treatment of HIV-1 infection, there is need for regimens that maximize long-term efficacy, safety, tolerability, and convenience. These features are determined by the specific formulation of the regimen (fixed-dose, or multi-tablet regimens), the nucleos(t)ide backbone, and the third agents (PI, NNRTI, or INSTI).

Switching to GS-9883/F/TAF may offer the advantages of a single-tablet FDC containing the unboosted, next-generation INSTI, GS-9883, combined with a TAF-containing nucleotide backbone. This regimen has the potential to avoid unwanted side effects from PI-based therapy (such as hyperbilirubinemia, rash, gastrointestinal upset, and dyslipidemia), decrease the potential for drug-drug interactions by removing the need for a boosting agent, avoiding potential long term renal and bone side effects from TDF, and avoiding potential long-term cardiovascular risk from ABC.
Four FDCs are currently approved in the US and EU for once-daily administration as a complete regimen for the treatment of HIV-1 infection, EFV/FTC/TDF, FTC/RPV/TDF, E/C/F/TDF, and ABC/DTG/3TC. There is no PI-containing FDC currently available. Studies have shown that a once-daily FDC significantly improved adherence, treatment satisfaction, and virologic outcomes for patients infected with HIV-1 [Dejesus E 2009], [Hodder et al 2010], [Airoldi et al 2010], [Bangsberg et al 2010]. Due to longer duration of high adherence, patients taking FDCs also have better clinical outcomes, such as fewer hospitalizations, compared with multiple-tablet regimens [Sax et al 2010].

Boosted protease inhibitors still represent a sizeable portion of the treated HIV-1-infected population and are viewed as the class with the greatest barrier to resistance. Boosted DRV is the only PI that remains on the DHHS treatment guidelines as a preferred agent, though ATV is still widely prescribed. Use of DRV/r and ATV/r in this study will allow comparison of the GS-9883/F/TAF FDC with these third agents, regardless of NRTI backbone. The study has the potential to demonstrate benefits such as decreased pill burden and adverse events, and improved patient reported outcomes.

This study will evaluate the safety, efficacy and tolerability of switching from boosted PI regimens to GS-9883/F/TAF, thereby assessing the viability of GS-9883/F/TAF as a FDC option for HIV-infected patients.

1.7. 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 IQ95 Values

<table>
<thead>
<tr>
<th>GS-9883 dose</th>
<th>N</th>
<th>Median (range) C_{tau,SS} (ng/mL)</th>
<th>Median (range) paIQ95a</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>4</td>
<td>206.5 (146.0 – 342.0)</td>
<td>1.3 (0.9 – 2.1)</td>
</tr>
<tr>
<td>25 mg</td>
<td>4</td>
<td>797.5 (714.0 – 1900.0)</td>
<td>4.9 (4.4 – 11.7)</td>
</tr>
<tr>
<td>50 mg</td>
<td>4</td>
<td>2170.0 (852.0 – 3020.0)</td>
<td>13.4 (5.3 – 18.6)</td>
</tr>
<tr>
<td>100 mg</td>
<td>4</td>
<td>4190.0 (3730.0 – 5970.0)</td>
<td>25.9 (23 – 36.9)</td>
</tr>
</tbody>
</table>

a The paIQ95 value is estimated based on steady-state C_{tau} values and the in vitro paIC95 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 (paIQ95) 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 paIQ95 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 paIQ95 of approximately 20, providing considerable coverage above the target concentration of 162 ng/mL (paIC95).

GS-9883 (75 mg) single agent coadministered with F/TAF (200/25 mg) is currently being evaluated in a Phase 2 study, GS-US-141-1475 (GS-9883+F/TAF vs DTG+F/TAF). The Week 24 data from this study support the safety and efficacy of GS-9883 exposures obtained with the 75 mg dose of the single agent.

GS-9883/F/TAF FDC Dose Selection

A fixed dose formulation of GS-9883/F/TAF was developed for use in Phase 3 studies. Preliminary results from the relative bioavailability (rBA) study (GS-US-141-1233) of GS-9883/F/TAF (75/200/25 mg) showed that GS-9883 plasma exposure was higher (with C_{max} and AUC_{inf} increase of 31% and 27%, respectively) following administration of the FDC as compared with exposure following administration of GS-9883 (75 mg) + F/TAF (200/25 mg) under fasted conditions. The increase in GS-9883 exposures associated with the FDC formulation results in an estimated mean paIQ95 of 24.3, compared to an estimated mean paIQ95 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.

1.8. Risk Benefit Assessment for this Study

All patients with HIV-1 infection should receive effective anti-retroviral therapy. Potential risks associated with all classes of ARVs include immune reconstitution syndrome, lipodystrophy, and lactic acidosis with steatosis. The risk of class effects is considered to be low. Important identified risks appropriately managed by study inclusion/exclusion criteria as well as through close clinical and laboratory monitoring during the study are as follows: hypersensitivity reaction to abacavir and allergy to any components of the tablets. Some observational studies have shown increased risk of cardiovascular disease with abacavir. Protease inhibitors may be associated with increased lipid levels and gastrointestinal side effects. If patients are currently infected with hepatitis B and discontinue their existing or new therapy, there is a risk of severe acute exacerbations of hepatitis B. Interim data will also be reviewed by an independent data monitoring committee. 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.

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 7.5.7).

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

1.9. Compliance

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

The primary objective of this study is:

- To evaluate the efficacy of switching to a FDC of GS-9883/F/TAF versus continuing on a regimen consisting of boosted atazanavir or darunavir plus either FTC/TDF or ABC/3TC in HIV-1 infected adult subjects who are virologically suppressed as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48

The secondary objective of this study is:

- To evaluate the safety and tolerability of the two treatment groups through Week 48
3. STUDY DESIGN

3.1. Endpoints

The primary efficacy endpoint is:

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

The secondary efficacy endpoints include:

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

3.2. Study Design

This protocol describes a randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of switching to a FDC of GS-9883/F/TAF in HIV-1 infected adult subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a regimen consisting of ritonavir or cobicistat boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months prior to screening.

3.3. Study Treatments

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

**Treatment Group 1:** Switch to FDC of GS-9883 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (GS-9883/F/TAF) administered orally, once daily without regard to food (n=260)

**Treatment Group 2:** Remain on current antiretroviral regimen consisting of ritonavir or cobicistat boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally, once daily with food (n=260)

3.4. Duration of Treatment

The treatment duration is 48 weeks.

At the Week 48 Visit, treatment group 1 and 2 subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC for an additional 96 weeks and attend study visits every 12 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.
Figure 3-1. Study Schema

Day 1

Screening ≤ 30 days prior to Day 1

Treatment Group 1: GS-9883/F/TAF FDC QD (n=260)

Treatment Group 2: Remain on current regimen of boosted ATV or DRV plus FTC/TDF or ABC/3TC QD (n=260)

Week 48

30 Day F/U

a. Following the Day 1 visit, subjects will be required to return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Week 48.

b. After Week 48, subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC for an additional 96 weeks and attend study visits every 12 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

c. Subjects who complete the study drug through the Week 48 Visit and do not wish to receive GS-9883/F/TAF FDC will be required to return to the clinic 30 days after the completion of study drugs for a 30-Day Follow-Up Visit.

3.5. Biomarker Testing

3.5.1. Biomarker Samples for Optional Pharmacogenomic Research

PPD
3.5.2.      Additional Sample Storage

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

4.1. Number of Subjects and Subject Selection

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

4.2. Inclusion Criteria

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

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

2. Age ≥ 18 years

3. Currently receiving a once daily antiretroviral regimen consisting of ritonavir or cobicistat boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months preceding the screening visit

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

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

6. Adequate renal function:
   Estimated glomerular filtration rate ≥ 50 mL/min (≥ 0.83 mL/sec) according to the Cockcroft-Gault formula {Cockcroft et al 1976}:
   a. Male: \[
   \frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = \text{CLcr (mL/min)}
   \]
   \[
   \frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in umol/L}) \times 0.6786} = \text{CLcr (mL/sec)}
   \]
   b. Female: \[
   \frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} \times 0.85 = \text{CLcr (mL/min)}
   \]
   \[
   \frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in umol/L}) \times 0.6786} = \text{CLcr (mL/sec)}
   \]

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

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

9. Adequate hematologic function (absolute neutrophil count ≥ 750/mm$^3$ (≥ 0.75 GI/L); platelets ≥ 50,000/mm$^3$ (≥ 50 GI/L); hemoglobin ≥ 8.5 g/dL (≥ 85 g/L))
10. Serum amylase ≤ 5 × ULN (subjects with serum amylase ≥ 5 × ULN will remain eligible if serum lipase is ≤ 5 × ULN)

11. Females of childbearing potential must agree to utilize protocol recommended highly effective contraceptive methods or be non-heterosexually active or practice sexual abstinence (as defined in Appendix 6) 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 6) throughout the study period and for 90 days following the last dose of study drug.

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

14. Life expectancy ≥ 1 year

15. Currently on a stable regimen for ≥ 6 months preceding the Screening visit with documented plasma HIV-1 RNA < 50 copies/mL for ≥ 6 months preceding the Screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL).

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

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

17. No previous use of any approved or experimental integrase strand transfer inhibitor (INSTI)

4.3. **Exclusion Criteria**

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

1. An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening (refer to Appendix 5)

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

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

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

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

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

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

9. Any known allergies to the excipients of GS-9883/F/TAF FDC or ATV, RTV, DRV, COBI, FTC/TDF or ABC/3TC

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 medications listed in the Table 5-1 and Table 5-2. Administration of any Prohibited Medication (Table 5-1 and Table 5-2) must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.

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

14. Chronic hepatitis B infection in subjects not on a TDF containing regimen, as determined by either:
   - Positive HBV surface antigen and negative HBV surface antibody, regardless of HBV core antibody status, at the screening visit
   - Positive HBV core antibody and negative HBV surface antibody, regardless of HBV surface antigen status, at the screening visit

15. Active tuberculosis infection
5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization

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

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

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

**Treatment Group 1**: Switch to a FDC of GS-9883/emtricitabine/tenofovir alafenamide (GS-9883/F/TAF) administered orally once daily without regard to food (n=260)

**Treatment Group 2**: Remain on current antiretroviral regimen consisting of ritonavir or cobicistat boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally once daily with food (n=260)

Randomization will be stratified by the prior treatment regimen group (ie, TDF containing regimens [ritonavir or cobicistat boosted ATV or DRV plus FTC/TDF] and non-TDF containing regimens [ritonavir or cobicistat boosted ATV or DRV plus ABC/3TC]) at screening.

Subjects randomized in Treatment Group 1 will be assigned study drug bottle numbers of GS-9883/F/TAF FDC at study visits by IWRS.

Investigators must provide a prescription to the subjects in Treatment Group 2. Those subjects are responsible for obtaining their ARV treatment prior to or during the study visit.

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 Tablets

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

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

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

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

5.2.3. Storage and Handling

Study drug GS-9883/F/TAF 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

GS-9883/F/TAF tablets will be provided by Gilead Sciences.

GS-9883/Emtricitabine/Tenofovir alafenamide (GS-9883/F/TAF) 50 mg/200 mg/25 mg FDC will be administered orally, once daily without regard to food at approximately the same time each day.

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

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

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

**Table 5-1. Prior and Concomitant Medications (GS-9883/F/TAF Regimen)**

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

* Administration of any of the above medications must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.
### Table 5-2. Prior and Concomitant Medications (Boosted ATV and DRV regimen)

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

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

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

Additionally, Investigators should refer to the current product/package inserts of the antiretroviral medications for contraindications related to their use.

### 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

Return and disposal of study drug GS-9883/F/TAF 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, smoking history and prior medications within 30 days of the screening visit.
- If available, obtain historical genotype(s) (not required for entry to study)
- 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 (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb)

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

- If positive HBsAg, reflex testing for plasma HBV DNA, HBeAg (if negative, reflex HBeAb), and quantitative HBsAg

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

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

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

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

6.2.2. Day 1 Assessments

The following evaluations are to be completed at the Day 1 Visit. **The Investigator must have confirmed subject’s 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), UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) and VAS Adherence Questionnaire to be completed by the subject. Subject is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2-microglobulin
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will not be able to participate
  - Urine storage sample for possible additional clinical testing
Blood sample collection for the following laboratory analyses:

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

- Whole blood sample for potential HIV DNA genotyping

- Subjects who meet the definition of HBV infection below at Screening Visit (positive serum HBsAg or Positive HBeAb with quantifiable HBV DNA), will have plasma HBV DNA tested.

Optional blood sample collection for the following laboratory analyses if pharmacogenomic consent is obtained
6.3. Randomization

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

6.4. Treatment Assessments (Week 4 -48)

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

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

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

- Review of AEs and changes in concomitant medications
- Complete physical examination (Weeks 24 and 48) (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- 12-lead ECG performed supine (Weeks 24 and 48)
- Short Form 36 Health Survey (SF-36), HIV Symptoms Distress Module, Work Productivity and Activity Impairment Questionnaire (WPAI) and UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) 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.
- VAS Adherence Questionnaire. Subject is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2-microglobulin (Weeks 24 and 48)
— Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be discontinued

— Urine storage sample for possible additional clinical testing

• Blood sample collection for the following laboratory analyses:

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

— Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed with all labs collected except metabolic assessments, for which the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments only. (Weeks 12, 24 and 48)

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

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

— Plasma HIV-1 RNA

— CD4+ cell count

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

— For subjects that 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, and 48)

■ 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: HBsAb, HBcAb, and HBsAg. Subjects who are HBsAg and/or HBcAb positive will have a reflex test for HBV DNA (viral load) (Week 48)

— Hepatitis C virus (HCVAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed (Week 48)
Pharmacokinetic Blood Collection for subjects who are on study drug in Treatment Group 1 only. 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 in Treatment Group 1:

- 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 blood sample collection. In the event a subject routinely takes their study drug in the evening, a single post-dose sample may be drawn at Weeks 4 and 12 as the subject will not be instructed to change their dosing time to accommodate this trough PK draw.

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

Optional Pharmacokinetic (PK) Substudy:
6.5. Treatment Assessments (Post Week 48)

6.5.1. Post Week 48 Assessments

At the Week 48 visit, subjects who completed 48 weeks of study drug treatment and are in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC for an additional 96 weeks and attend study visits every 12 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

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

Subjects participating in the study post Week 48 will be required to return for study visits according to the schedule presented in Appendix 1. Study Procedures Table and described in the text below:

- Review of AEs and changes in concomitant medications
- Complete physical examination (Every 48 weeks) (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- 12-lead ECG performed supine (Every 48 weeks)
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2-microglobulin (Every 24 weeks)
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be discontinued.
  - Urine storage sample for possible additional clinical testing
Blood sample collection for the following laboratory analyses:

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

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

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

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

- Plasma HIV-1 RNA

- CD4+ cell count

- Plasma storage sample for safety, virology or PK testing

- For subjects that 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: HBsAb, HBCab, and 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 Section 6.13.

- Document study drug dispensation and accountability for all study drugs dispensed.
6.6. Post-treatment Assessments

6.6.1. Early Study Drugs Discontinuation Assessments

If the subject discontinues study drug, 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.

Subjects who complete the study drug through Week 48 and who do not continue participation in the study, will not be required to complete 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)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- 12-lead ECG performed supine (for discontinuation visits up to Week 48 only)
- VAS Adherence Questionnaire. Subject is to read questionnaire by himself/herself and write/make 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
  - 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)
— HIV-1 genotype/phenotype testing for subjects with virologic failure

• Drug accountability

6.6.2. 30-Day Follow-Up

If the subject discontinues study drug, the subject will be required to return to the clinic 30 days after the completion of the Early Study Drugs Discontinuation Visit for the 30-Day Follow-Up visit.

Subjects who complete the study drug through Week 48 and who do not further continue participation in the study, will be required to return to the clinic 30 days after the completion of study drug for the 30-Day Follow-Up visit.

Those subjects who prematurely discontinue study drug 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.

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

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

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

6.7. Criteria for Discontinuation of Study Treatment

Study medication will be discontinued in the following instances:

• Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject’s best interest

• Subject request to discontinue for any reason

• Pregnancy during the study; refer to Appendix 6

• 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. Other Evaluations

6.8.1. Markers of Renal Tubular Function

For all subjects, urine will be collected for selected evaluations of renal tubular function, which will include but not be limited to urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2-microglobulin at Day 1 Visit, Weeks 24, 48, and every 24 weeks post Week 48. Samples may be stored for a period of 15 years at the end of the study.

6.9. Blood and Urine Storage

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

6.10. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.7, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.11. End of Study

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

6.12. Post Study Care

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

6.13. Virologic Failure

Virologic failure is defined as virologic rebound or having HIV-1 RNA \( \geq 50 \text{ copies/mL} \) at study drug discontinuation or Week 48.

6.13.1. Management of Virologic Rebound

Subjects who meet the criteria listed below will be considered to have virologic rebound:
• At any post Day 1 visit, a rebound in HIV-1 RNA ≥ 50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit;

OR

• Any subject with HIV RNA ≥ 50 copies/mL at study drug discontinuation

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

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

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

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

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

<table>
<thead>
<tr>
<th>Screening</th>
<th>Treatment Period</th>
<th>30-Day Follow-up</th>
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<tr>
<td>Day 1</td>
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<tr>
<td></td>
<td>At any post Day 1 visit, a rebound in HIV-1 RNA to ≥ 50 copies/mL</td>
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<tr>
<td>Unconfirmed virologic rebound; remain on current regimen a</td>
<td>Return for scheduled/unscheduled HIV-1 RNA and potential genotype/phenotype sampling (2-3 weeks later)</td>
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<tr>
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<tr>
<td>Confirmed virologic rebound and HIV-1 Genotype and Phenotype b, c</td>
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<tr>
<td>If no reverse transcriptase, protease or integrase resistance detected, may continue on study drugs d</td>
<td>Remain on study</td>
<td>If reverse transcriptase, protease or integrase resistance detected, discontinue study drugs and construct a new ARV regimen e</td>
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</tbody>
</table>

a. If virologic rebound is not confirmed, the subject will remain on their current regimen.
b. If virologic rebound is confirmed and the HIV-1 RNA is ≥ 200 copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase) will be analyzed.
c. Based on the results of the genotypic and phenotypic assays, the subject will remain on study drugs or study drugs will be discontinued. If genotyping or phenotyping 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.

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

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

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

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

7.1.1. Adverse Events

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

An AE does not include the following:

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

7.1.2. Serious Adverse Events

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

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

• A congenital anomaly/birth defect

• A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is 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 sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

• No: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

• Yes: There is reasonable possibility that the event may have been caused by the investigational medicinal product.
It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

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

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

7.2.2. Assessment of Severity

AE severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4). For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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

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

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

Requirements for collection prior to study drug initiation:

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

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

7.3.1. Adverse Events

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

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

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

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

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

- If it is not possible to record and submit the SAE information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the SAE on the paper serious adverse event reporting form and submit by email or fax within 24 hours of the investigator’s knowledge of the event to:

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

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

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

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

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

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject’s CRF/eCRF and the event description section of the SAE form.
• For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

7.4. Gilead Reporting Requirements

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

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

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

7.5. Toxicity Management

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

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

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

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

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the Investigator.
7.5.2. Grade 3 Laboratory Abnormality or Clinical Event

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

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

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

7.5.3. Grade 4 Laboratory Abnormality or Clinical Event

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

- Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 CK after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product requires discussion with the Gilead Sciences Medical Monitor.

7.5.4. 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 × Day 1 value and >10 × 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 × Day 1 value and > 10 × ULN, the following is recommended:

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

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

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

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

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

**Elevated Liver Enzymes, Elevated Liver Function Tests**

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

During monitoring, if the ALT values and the liver function tests remain persistently elevated, the Investigator should discuss with the Gilead Medical Monitor whether the study drug should be discontinued.
7.5.4.2. 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 $> \text{ULN}$) 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 Hyperbilirubinemia

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

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

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

- Confirmed hyperbilirubinemia $> 10$ x ULN will require discontinuation.

- Elevation of conjugated (direct) bilirubin $> 2$ mg/dL in association with Grade 2 ALT or AST elevation will require discontinuation.
7.5.6. Management of Possible Abacavir Hypersensitivity Reaction

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

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

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

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

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

7.5.7. 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.

7.5.8. 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 feel the need 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. Instruction for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

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

Refer to the 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 Sections 7.3.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

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

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

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

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

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.
Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

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

Refer to Section 7.6.2.1 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 switching to a FDC of GS-9883/F/TAF versus continuing on a regimen consisting of boosted ATV or DRV plus either FTC/TDF or ABC/3TC (i.e., boosted PI + 2NRTIs) in HIV-1 infected subjects who are virologically suppressed as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48.

The secondary objective of this study is to evaluate the safety and tolerability of the two treatment groups through Week 48.

8.1.2. Primary Endpoint

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

8.1.3. Secondary Endpoint

The secondary endpoints include:

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

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All randomized

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

8.2.1.2. Efficacy

8.2.1.2.1. Full Analysis Set (FAS)

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

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

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

- Subjects who do not have on-treatment HIV-1 RNA in the Week 48 analysis window, except when missing is due to discontinuation of study drug for lack of efficacy.
- Subjects who do not meet the inclusion criterion for no previous use of any approved or experimental integrase strand transfer inhibitor (INSTI)
- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the Table 5-1 and Table 5-2.

8.2.1.3. Safety

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

8.2.1.4. Pharmacokinetics

8.2.1.4.1. Pharmacokinetic (PK) Substudy Analysis Set

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

8.2.1.4.2. Pharmacokinetic (PK) Analysis Set

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

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

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

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit plus or minus one significant digit, respectively (e.g., 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 (i.e., 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, and 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

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

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

- **HIV-1 RNA < 50 copies/mL**: this includes subjects who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 48 analysis window

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

- **No Virologic Data in the Week 48 Analysis Window**: this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window because of the following:
  - Discontinuation of study drug prior to or in the Week 48 analysis window due to reasons other than lack of efficacy and the last available on-treatment HIV-1 RNA is < 50 copies/mL, or
  - Missing data during the window but on study drug

8.5.1.2. Analysis of Primary Efficacy Endpoint

The null hypothesis is that the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 in the GS-9883/F/TAF group is at least 4% higher than that in the boosted PI + 2NRTIs group; the alternative hypothesis is that the proportion of subjects with HIV-1 RNA ≥50 copies/mL in the GS-9883/F/TAF group is less than 4% higher than that in the boosted-PI + 2NRTIs group.

Non-inferiority will be assessed using the confidence interval (CI) approach. The point estimate of treatment difference (GS-9883/F/TAF – boosted PI + 2NRTIs) and the associated 2-sided 95% CIs will be constructed based on the exact method. It will be concluded that GS-9883/F/TAF is non-inferior to boosted PI + 2NRTIs if the upper bound of the 2-sided 95%
CI of the difference between treatment groups (GS-9883/F/TAF – boosted PI + 2NRTIs) in the percentage of subjects with HIV-1 RNA \(\geq 50\) copies/mL is less than 4% (ie, a margin of 4% is applied to non-inferiority assessment).

If non-inferiority of GS-9883/F/TAF to boosted PI + 2NRTIs is established, the upper bound of the 95% CI will be compared to 0; if the upper bound of the 95% CI is less than 0, superiority of GS-9883/F/TAF over boosted PI + 2NRTIs will be established.

**8.5.2. Secondary Analyses**

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

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

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

**8.6. Safety Analysis**

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

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

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

**8.6.1. Extent of Exposure**

A subject’s extent of exposure to study drug will be generated from the study drug administration page in CRF. 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 5.

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the grading scheme defined in Grading of laboratory abnormalities attached in Appendix 4.

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

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

8.6.4. 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 ($C_{\text{max}}$, $T_{\text{max}}$, $C_{\text{tau}}$, $\text{AUC}_{\text{tau}}$, and $T_{\frac{1}{2}}$, as appropriate) may be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation %, SD, median, Q1, Q3, minimum, and maximum). Plasma concentrations over time will be plotted in semi-logarithmic and linear formats as mean ± standard deviation, and median (Q1, Q3).

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

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

8.8. Patient Reported Outcomes (PRO)

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

8.9. Sample Size

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

8.10. Independent Data Monitoring Committee

An external Independent Data Monitoring Committee (IDMC) will review the progress, efficacy, and safety data of this study while the study is ongoing. The committee will convene after approximately the first 30% subjects enrolled have completed Week 12 of the study or prematurely discontinued from the study drug, and will also convene after all subjects have completed Week 24 of the study or prematurely discontinued from study drug. However, Gilead will defer to the IDMC for any decision to convene earlier or more frequently. The IDMC will examine the safety results of the trial and also focus on logistical issues such as accrual, retention, quality of clinical and laboratory data, and implications of results of external studies.

No formal stopping rules will be used by the IDMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of adverse events associated with a study regimen warrant the early termination of the study in the best interest of the participants.
For each IDMC analysis performed prior to analysis for the primary efficacy endpoint, an alpha penalty of 0.00001 will be applied for the primary analysis of the primary efficacy endpoint.

8.11. Analysis Schedule

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

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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


The investigator 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 eCRF casebook will only capture the data required per the protocol schedule of events and procedures. 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(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

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

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

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

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

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

### 9.3. Joint Investigator/Sponsor Responsibilities

#### 9.3.1. Payment Reporting

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

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

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

9.3.3. **Access to Information for Auditing or Inspections**

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

9.3.4. **Study Discontinuation**

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


Bangsberg DR, Ragland K, Monk A, Deeks SG. A one-pill, once-daily, fixed-dose combination (FDC) of efavirenz, emtricitabine, and tenofovir disoproxil fumarate (EFV/FTC/TDF) regimen is associated with higher unannounced pill count adherence than non-one pill, once-daily [Poster]. 17th Conference on Retroviruses and Opportunistic Infections (CROI); 2010 February 16-19; San Francisco, CA.


Sax PE, Meyers J, Mugavero M, Davis KL. Adherence to Antiretroviral Treatment Regimens and Correlation with Risk of Hospitalization Among Commercially Insured HIV Patients in the United States [Poster O113]. 10th International Congress on Drug Therapy in HIV Infection; 2010 November 7-11; Glasgow, UK.


11. APPENDICES

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Appendix 4. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities
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Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults

GS-US-380-1878 Amendment 2, 19 October 2016

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

Erin Quirk, MD

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

CONFIDENTIAL  
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19 October 2016
## Appendix 2. Study Procedures Table

<table>
<thead>
<tr>
<th>Study Procedures</th>
<th>Screening&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Day 1&lt;sup&gt;b&lt;/sup&gt;</th>
<th>End of Week&lt;sup&gt;c, v&lt;/sup&gt;</th>
<th>Post-Week 48&lt;sup&gt;c, w&lt;/sup&gt;</th>
<th>30-Day Follow-up&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Early Study Drugs DC&lt;sup&gt;c&lt;/sup&gt;</th>
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<td><strong>Complete/Symptom-Directed Physical Exam</strong></td>
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<td>12-Lead ECG (performed supine)</td>
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<td>X&lt;sup&gt;m&lt;/sup&gt;</td>
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<tr>
<td>SF-36, HIV Symptoms Distress Module, WPAI, and UCLA SCTR GIT 2.0 Questionnaires</td>
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<td>VAS Adherence Questionnaire</td>
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<td>Height</td>
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<td>Vital signs (blood pressure, pulse, respiration rate, and temperature), including Weight</td>
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<td>Metabolic Assessments&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
<td>Plasma HIV-1 RNA</td>
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<tr>
<td>Study Procedures</td>
<td>Screening</td>
<td>Day 1</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>24</td>
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<td>Evaluation of renal tubular function</td>
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<td>Plasma and Urine Storage Sample</td>
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| HCV Serology                                           | X         | X     |   |   |    |    |    |    | X             | X^
| HIV-1 Genotype/Phenotype                               | X         |       |   |   |    |    |    |    |                | X                 |                    |
| Single PK Sample                                       | X         | X     | X | X | X  | X  |     |     |                |                    |                    |
| Trough and post dose PK Sample                         | X         |       | X |   |    |    |    |    |                |                    |                    |
| Optional PPD                                           | X         |       |   |   |    |    |    |    |                |                    |                    |
| Randomization                                          |           | X     |   |   |    |    |    |    |                |                    |                    |
| Provide subject dosing diary to Treatment Group        | X         | X     | X | X | X  | X  |     |     |                |                    |                    |
| Optional PK Substudy                                   |           | X     |   |   |    |    |    |    |                |                    |                    |
| HBV blood panel                                        | X^a       |       |   |   | X  | X  | X  | X  |                |                    |                    |
| Plasma HBV DNA                                        | X         | X     | X | X | X  | X  | X  | X  |                |                    | X                  |
| Study Drug Dispensation                                | X         | X     | X | X | X  | X  | X  | X  | X             |                    |                    |
| Study Drug Accountability                              |           | 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 on 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 Week 48 Visit even if the subject discontinues study drug.

**d.** Symptom-directed physical examination as needed.

**e.** HIV-1 genotype and phenotype testing for subjects with virologic failure. Following virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Sections 6.13).

**f.** Any adverse event or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

**g.** Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
h. Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) At Day 1, Weeks 12, 24, 48 and every 24 weeks post Week 48, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. Additionally, TSH will be analyzed at Screening, Day 1, Weeks 24, 48, followed by every 24 weeks post Week 48, and Early Study Drugs Discontinuation visit. PT/INR will be performed at Day 1.

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

j. Every 24 weeks post Week 48 Visit

k. CBC with differential and platelet count.

l. Evaluation of renal tubular function includes analyses of urine albumin, urine creatinine, urine protein, retinol binding protein and beta-2-microglobulin

m. To be performed every 48 weeks post Week 48 Visit

n. A single PK blood sample will be collected at any time pre or post dose from subjects in Treatment Group 1.

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

p. A PK substudy will be performed in a subset of Treatment Group 1 subjects (n=24) at selected study sites. The pharmacokinetic substudy visit must occur at the Week 4 or Week 8 visits. The substudy will include intensive PK profiling in plasma.

q. HBV blood panel will be performed at Screening (Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBeAb)).

r. To be performed for subjects who meet the definition of HBV infection

s. At Weeks 12, 24, 48, 72, 96, and 120, for subjects who meet the definition of HBV infection at any visit, the following will be performed by the central laboratory: HBsAb, HBsAg (qualitative and quantitative) and HBeAg (if negative reflex, HBeAb).

t. Study drug GS-9883/F/TAF to be dispensed to Treatment Group 1 subjects.

u. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used. Those subjects who prematurely discontinue study drug 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.

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

w. Visit window of ± 6 days for study visits post Week 48.

x. GS-9883/F/TAF FDC will be dispensed to subjects participating in the study post Week 48 visit.

y. 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.

z. At Weeks 48, 96 and 144, for subjects who do NOT meet the definition of HBV infection at any visit, the following will be performed by the central laboratory: HBsAg, HBsAb, and HBeAb. Subjects who are HBsAg and/or HBeAb positive will have a reflex test for HBV DNA (viral load).

aa. A complete physical exam should be done every 48 weeks post Week 48 Visit.

bb. Only to be completed for Early Study Drugs Discontinuation Visits up to Week 48.
Appendix 3. Management of Clinical and Laboratory Adverse Events

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>May continue dosing at the discretion of the investigator</td>
<td>Repeat lab to confirm toxicity grade</td>
<td>Repeat lab to confirm toxicity grade</td>
<td>If confirmed and possibly or probably related to investigational medicinal products, dosing may continue at the discretion of the investigator</td>
</tr>
</tbody>
</table>

If confirmed and possibly and/or probably related to investigational medicinal products:

1. Withhold investigational medicinal products until ≤ Grade 2
2. Restart all investigational medicinal products at full dose

If Grade 3 or 4 recurrence that is confirmed and possibly or probably related to investigational medicinal products, discontinue all investigational medicinal products dosing permanently

If Grade 3 or 4 recurrence that is considered unrelated to investigational medicinal products, continue all investigational medicinal products dosing permanently at the same dose at the discretion of the investigator
## Appendix 4. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

**Antiviral Toxicity Grading Scale Version: 01 April 2015**

### HEMATOLOGY

<table>
<thead>
<tr>
<th>Test</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV POSITIVE Adult and Pediatric ≥ 57 Days</td>
<td>8.5 to 10.0 g/dL</td>
<td>7.5 to &lt; 8.5 g/dL</td>
<td>6.5 to &lt; 7.5 g/dL</td>
<td>&lt; 6.5 g/dL</td>
</tr>
<tr>
<td>HIV POSITIVE Adult and Pediatric ≥ 57 Days</td>
<td>85 to 100 g/L</td>
<td>75 to &lt; 85 g/L</td>
<td>65 to &lt; 75 g/L</td>
<td>&lt; 65 g/L</td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>10.0 to 10.9 g/dL</td>
<td>9.0 to &lt; 10.0 g/dL</td>
<td>7.0 to &lt; 9.0 g/dL</td>
<td>&lt; 7.0 g/dL</td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>100 to 109 g/L</td>
<td>90 to &lt; 100 g/L</td>
<td>70 to &lt; 90 g/L</td>
<td>&lt; 70 g/L</td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>OR Any decrease from Baseline</td>
<td>OR</td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>2.5 to &lt; 3.5 g/dL</td>
<td>3.5 to &lt; 4.5 g/dL</td>
<td>≥ 4.5 g/dL</td>
<td></td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>25 to &lt; 35 g/L</td>
<td>35 to &lt; 45 g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>10.0 to 10.9 g/dL</td>
<td>9.0 to &lt; 10.0 g/dL</td>
<td>7.0 to &lt; 9.0 g/dL</td>
<td>&lt; 7.0 g/dL</td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>85 to 100 g/L</td>
<td>75 to &lt; 85 g/L</td>
<td>65 to &lt; 75 g/L</td>
<td>&lt; 65 g/L</td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>OR Any decrease from Baseline</td>
<td>OR</td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>2.5 to &lt; 3.5 g/dL</td>
<td>3.5 to &lt; 4.5 g/dL</td>
<td>≥ 4.5 g/dL</td>
<td></td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>25 to &lt; 35 g/L</td>
<td>35 to &lt; 45 g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>10.0 to 10.9 g/dL</td>
<td>9.0 to &lt; 10.0 g/dL</td>
<td>7.0 to &lt; 9.0 g/dL</td>
<td>&lt; 7.0 g/dL</td>
</tr>
<tr>
<td>HIV NEGATIVE Adult and Pediatric ≥ 57 Days</td>
<td>100 to 109 g/L</td>
<td>90 to &lt; 100 g/L</td>
<td>70 to &lt; 90 g/L</td>
<td>&lt; 70 g/L</td>
</tr>
<tr>
<td>INFANT, 36–56 Days (HIV POSITIVE OR NEGATIVE)</td>
<td>8.5 to 9.4 g/dL</td>
<td>7.0 to &lt; 8.5 g/dL</td>
<td>6.0 to &lt; 7.0 g/dL</td>
<td>&lt; 6.0 g/dL</td>
</tr>
<tr>
<td>INFANT, 36–56 Days (HIV POSITIVE OR NEGATIVE)</td>
<td>85 to 94 g/L</td>
<td>70 to &lt; 85 g/L</td>
<td>60 to &lt; 70 g/L</td>
<td>&lt; 60 g/L</td>
</tr>
<tr>
<td>INFANT, 22–35 Days (HIV POSITIVE OR NEGATIVE)</td>
<td>9.5 to 10.5 g/dL</td>
<td>8.0 to &lt; 9.5 g/dL</td>
<td>7.0 to &lt; 8.0 g/dL</td>
<td>&lt; 7.0 g/dL</td>
</tr>
<tr>
<td>INFANT, 22–35 Days (HIV POSITIVE OR NEGATIVE)</td>
<td>95 to 105 g/L</td>
<td>80 to &lt; 95 g/L</td>
<td>70 to &lt; 80 g/L</td>
<td>&lt; 70 g/L</td>
</tr>
<tr>
<td>INFANT, 1–21 Days (HIV POSITIVE OR NEGATIVE)</td>
<td>12.0 to 13.0 g/dL</td>
<td>10.0 to &lt; 12.0 g/dL</td>
<td>9.0 to &lt; 10.0 g/dL</td>
<td>&lt; 9.0 g/dL</td>
</tr>
<tr>
<td>INFANT, 1–21 Days (HIV POSITIVE OR NEGATIVE)</td>
<td>120 to 130 g/L</td>
<td>100 to &lt; 120 g/L</td>
<td>90 to &lt; 100 g/L</td>
<td>&lt; 90 g/L</td>
</tr>
<tr>
<td>Absolute Neutrophil Count (ANC) Adult and Pediatric, ≥ 7 Months#</td>
<td>1000 to 1300/mm³</td>
<td>750 to &lt; 1000/mm³</td>
<td>500 to &lt; 750/mm³</td>
<td>&lt; 500/mm³</td>
</tr>
<tr>
<td>Absolute Neutrophil Count (ANC) Adult and Pediatric, ≥ 7 Months#</td>
<td>1.00 to 1.30 GI/L</td>
<td>0.75 to &lt; 1.00 GI/L</td>
<td>0.50 to &lt; 0.75 GI/L</td>
<td>&lt; 0.50 GI/L</td>
</tr>
</tbody>
</table>
## HEMATOLOGY

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute CD4+ Count</strong> HIV NEGATIVE ONLY Adult and Pediatric &gt; 13 Years</td>
<td>300 to 400/mm^3 300 to 400/μL</td>
<td>200 to &lt; 300/mm^3 200 to &lt; 300/μL</td>
<td>100 to &lt; 200/mm^3 100 to &lt; 200/μL</td>
<td>&lt; 100/mm^3  &lt; 100/μL</td>
</tr>
<tr>
<td><strong>Absolute Lymphocyte Count</strong> HIV NEGATIVE ONLY Adult and Pediatric &gt; 13 Years</td>
<td>600 to 650/mm^3 0.60 to 0.65 GI/L</td>
<td>500 to &lt; 600/mm^3 0.50 to &lt; 0.60 GI/L</td>
<td>350 to &lt; 500/mm^3 0.35 to &lt; 0.50 GI/L</td>
<td>&lt; 350/mm^3  &lt; 0.35 GI/L</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td>100,000 to &lt; 125,000/mm^3 100 to &lt; 125 GI/L</td>
<td>50,000 to &lt; 100,000/mm^3 50 to &lt; 100 GI/L</td>
<td>25,000 to &lt; 50,000/mm^3 25 to &lt; 50 GI/L</td>
<td>&lt; 25,000/mm^3  &lt; 25 GI/L</td>
</tr>
<tr>
<td><strong>WBCs</strong></td>
<td>2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L</td>
<td>1,500 to &lt; 2,000/mm^3 1.50 to &lt; 2.00 GI/L</td>
<td>1000 to &lt; 1,500/mm^3 1.00 to &lt; 1.50 GI/L</td>
<td>&lt; 1000/mm^3  &lt; 1.00 GI/L</td>
</tr>
<tr>
<td><strong>Hypofibrinogenemia</strong></td>
<td>100 to 200 mg/dL 1.00 to 2.00 g/L</td>
<td>75 to &lt; 100 mg/dL 0.75 to &lt; 1.00 g/L</td>
<td>50 to &lt; 75 mg/dL 0.50 to &lt; 0.75 g/L</td>
<td>&lt; 50 mg/dL  &lt; 0.50 g/L</td>
</tr>
<tr>
<td><strong>Hyperfibrinogenemia</strong></td>
<td>&gt; ULN to 600 mg/dL &gt; ULN to 6.0 g/L</td>
<td>&gt; 600 mg/dL &gt; 6.0 g/L</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Fibrin Split Product</strong></td>
<td>20 to 40 μg/mL 20 to 40 mg/L</td>
<td>&gt; 40 to 50 μg/mL &gt; 40 to 50 mg/L</td>
<td>&gt; 50 to 60 μg/mL &gt; 50 to 60 mg/L</td>
<td>&gt; 60 μg/mL &gt; 60 mg/L</td>
</tr>
<tr>
<td><strong>Prothrombin Time (PT)</strong></td>
<td>&gt; 1.00 to 1.25 × ULN</td>
<td>&gt; 1.25 to 1.50 × ULN</td>
<td>&gt; 1.50 to 3.00 × ULN</td>
<td>&gt; 3.00 × ULN</td>
</tr>
<tr>
<td><strong>International Normalized Ratio of prothrombin time (INR)</strong></td>
<td>1.1 to 1.5 x ULN</td>
<td>&gt;1.5 to 2.0 x ULN</td>
<td>&gt;2.0 to 3.0 x ULN</td>
<td>&gt;3.0 x ULN</td>
</tr>
</tbody>
</table>
### HEMATOLOGY

<table>
<thead>
<tr>
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<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Partial</td>
<td>&gt; 1.00 to 1.66 × ULN</td>
<td>&gt; 1.66 to 2.33 × ULN</td>
<td>&gt; 2.33 to 3.00 × ULN</td>
<td>&gt; 3.00 × ULN</td>
</tr>
<tr>
<td>Thromboplastin Time (APTT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methemoglobin</td>
<td>5.0 to 10.0%</td>
<td>&gt; 10.0 to 15.0%</td>
<td>&gt; 15.0 to 20.0%</td>
<td>&gt; 20.0%</td>
</tr>
</tbody>
</table>

# 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.
<table>
<thead>
<tr>
<th>CHEMISTRY</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>130 to &lt;LLN mEq/L</td>
<td>125 to &lt; 130 mEq/L</td>
<td>121 to &lt; 125 mEq/L</td>
<td>&lt; 121 mEq/L</td>
</tr>
<tr>
<td></td>
<td>130 to &lt;LLN mmol/L</td>
<td>125 to &lt; 130 mmol/L</td>
<td>121 to &lt; 125 mmol/L</td>
<td>&lt; 121 mmol/L</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>&gt;ULN to 150 mEq/L</td>
<td>&gt; 150 to 154 mEq/L</td>
<td>&gt; 154 to 159 mEq/L</td>
<td>&gt; 159 mEq/L</td>
</tr>
<tr>
<td></td>
<td>&gt;ULN to 150 mmol/L</td>
<td>&gt; 150 to 154 mmol/L</td>
<td>&gt; 154 to 159 mmol/L</td>
<td>&gt; 159 mmol/L</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3.0 to &lt;LLN mEq/L</td>
<td>2.5 to &lt; 3.0 mEq/L</td>
<td>2.0 to &lt; 2.5 mEq/L</td>
<td>&lt; 2.0 mEq/L</td>
</tr>
<tr>
<td>Adult and Pediatric</td>
<td>3.0 to &lt;LLN mmol/L</td>
<td>2.5 to &lt; 3.0 mmol/L</td>
<td>2.0 to &lt; 2.5 mmol/L</td>
<td>&lt; 2.0 mmol/L</td>
</tr>
<tr>
<td>≥ 1 Year</td>
<td>3.0 to 3.4 mEq/L</td>
<td>2.5 to &lt; 3.0 mEq/L</td>
<td>2.0 to &lt; 2.5 mEq/L</td>
<td>&lt; 2.0 mEq/L</td>
</tr>
<tr>
<td></td>
<td>3.0 to 3.4 mmol/L</td>
<td>2.5 to &lt;3.0 mmol/L</td>
<td>2.0 to &lt;2.5 mmol/L</td>
<td>&lt; 2.0 mmol/L</td>
</tr>
<tr>
<td>Infant &lt;1 Year</td>
<td>&gt;ULN to 6.0 mEq/L</td>
<td>&gt; 6.0 to 6.5 mEq/L</td>
<td>&gt; 6.5 to 7.0 mEq/L</td>
<td>&gt; 7.0 mEq/L</td>
</tr>
<tr>
<td>Adult and Pediatric</td>
<td>&gt;ULN to 6.0 mmol/L</td>
<td>&gt; 6.0 to 6.5 mmol/L</td>
<td>&gt; 6.5 to 7.0 mmol/L</td>
<td>&gt; 7.0 mmol/L</td>
</tr>
<tr>
<td>≥ 1 Year</td>
<td>&gt;ULN to 6.0 mEq/L</td>
<td>&gt; 6.0 to 6.5 mEq/L</td>
<td>&gt; 6.5 to 7.0 mEq/L</td>
<td>&gt; 7.0 mEq/L</td>
</tr>
<tr>
<td></td>
<td>&gt;ULN to 6.0 mmol/L</td>
<td>&gt; 6.0 to 6.5 mmol/L</td>
<td>&gt; 6.5 to 7.0 mmol/L</td>
<td>&gt; 7.0 mmol/L</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>55 to 64 mg/dL</td>
<td>40 to &lt; 55 mg/dL</td>
<td>30 to &lt; 40 mg/dL</td>
<td>&lt; 30 mg/dL</td>
</tr>
<tr>
<td>Adult and Pediatric</td>
<td>3.03 to 3.58 mmol/L</td>
<td>2.20 to &lt; 3.03 mmol/L</td>
<td>1.64 to &lt; 2.20 mmol/L</td>
<td>&lt; 1.64 mmol/L</td>
</tr>
<tr>
<td>≥ 1 Month</td>
<td>55 to 64 mg/dL</td>
<td>40 to &lt; 55 mg/dL</td>
<td>30 to &lt; 40 mg/dL</td>
<td>&lt; 30 mg/dL</td>
</tr>
<tr>
<td></td>
<td>3.03 to 3.58 mmol/L</td>
<td>2.20 to &lt; 3.03 mmol/L</td>
<td>1.64 to &lt; 2.20 mmol/L</td>
<td>&lt; 1.64 mmol/L</td>
</tr>
<tr>
<td>Infant, &lt;1 Month</td>
<td>50 to 54 mg/dL</td>
<td>40 to &lt; 50 mg/dL</td>
<td>30 to &lt; 40 mg/dL</td>
<td>&lt; 30 mg/dL</td>
</tr>
<tr>
<td></td>
<td>2.8 to 3.0 mmol/L</td>
<td>2.2 to &lt; 2.8 mmol/L</td>
<td>1.7 to &lt; 2.2 mmol/L</td>
<td>&lt; 1.7 mmol/L</td>
</tr>
</tbody>
</table>
## CHEMISTRY

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperglycemia, Nonfasting</strong></td>
<td>116 to 160 mg/dL, 6.42 to 8.91 mmol/L</td>
<td>&gt; 160 to 250 mg/dL, 8.91 to 13.90 mmol/L</td>
<td>&gt; 250 to 500 mg/dL, 13.90 to 27.79 mmol/L</td>
<td>&gt; 500 mg/dL, 27.79 mmol/L</td>
</tr>
<tr>
<td><strong>Hyperglycemia, Fasting</strong></td>
<td>110 to 125 mg/dL, 6.08 to 6.96 mmol/L</td>
<td>&gt;125 to 250 mg/dL, 6.96 to 13.90 mmol/L</td>
<td>&gt;250 to 500 mg/dL, 13.90 to 27.79 mmol/L</td>
<td>&gt;500 mg/dL, 27.79 mmol/L</td>
</tr>
<tr>
<td><strong>Hypocalcemia</strong> (corrected for albumin if appropriate*)</td>
<td>7.8 &lt; LLN mg/dL, 1.94 to &lt; LLN mmol/L</td>
<td>7.0 to &lt; 7.8 mg/dL, 1.74 to &lt; 1.94 mmol/L</td>
<td>6.1 to &lt; 7.0 mg/dL, 1.51 to &lt; 1.74 mmol/L</td>
<td>&lt; 6.1 mg/dL, &lt; 1.51 mmol/L</td>
</tr>
<tr>
<td><strong>Pediatric ≥ 7 days - 2 Years</strong></td>
<td>7.8 to 8.4 mg/dL, 1.94 to 2.10 mmol/L</td>
<td>7.0 to &lt; 7.8 mg/dL, 1.74 to &lt; 1.94 mmol/L</td>
<td>6.1 to &lt; 7.0 mg/dL, 1.51 to &lt; 1.74 mmol/L</td>
<td>&lt; 6.1 mg/dL, &lt; 1.51 mmol/L</td>
</tr>
<tr>
<td><strong>Infant, &lt; 7 Days</strong></td>
<td>6.5 to 7.5 mg/dL, 1.61 to 1.88 mmol/L</td>
<td>6.0 to &lt; 6.5 mg/dL, 1.49 to &lt; 1.61 mmol/L</td>
<td>5.5 to &lt; 6.0 mg/dL, 1.36 to &lt; 1.49 mmol/L</td>
<td>&lt; 5.5 mg/dL, &lt; 1.36 mmol/L</td>
</tr>
<tr>
<td><em><em>Hypercalcemia (corrected for albumin if appropriate</em>)</em>*</td>
<td>&gt; ULN to 11.5 mg/dL, &gt; ULN to 2.88 mmol/L</td>
<td>&gt; 11.5 to 12.5 mg/dL, &gt; 2.88 to 3.13 mmol/L</td>
<td>&gt; 12.5 to 13.5 mg/dL, &gt; 3.13 to 3.38 mmol/L</td>
<td>&gt; 13.5 mg/dL, &gt; 3.38 mmol/L</td>
</tr>
<tr>
<td><strong>Infant, &lt; 7 Days</strong></td>
<td>11.5 to 12.4 mg/dL, 2.86 to 3.10 mmol/L</td>
<td>&gt; 12.4 to 12.9 mg/dL, &gt; 3.10 to 3.23 mmol/L</td>
<td>&gt; 12.9 to 13.5 mg/dL, &gt; 3.23 to 3.38 mmol/L</td>
<td>&gt; 13.5 mg/dL, &gt; 3.38 mmol/L</td>
</tr>
<tr>
<td><strong>Hypocalcemia (ionized)</strong></td>
<td>3.0 mg/dL to &lt; LLN, 0.74 mmol/L to &lt; LLN</td>
<td>2.5 to &lt; 3.0 mg/dL, 0.62 to &lt; 0.74 mmol/L</td>
<td>2.0 to &lt; 2.5 mg/dL, 0.49 to &lt; 0.62 mmol/L</td>
<td>&lt; 2.0 mg/dL, &lt; 0.49 mmol/L</td>
</tr>
<tr>
<td><strong>Hypercalcemia (ionized)</strong></td>
<td>&gt; ULN to 6.0 mg/dL, &gt; ULN to 1.50 mmol/L</td>
<td>&gt; 6.0 to 6.5 mg/dL, &gt; 1.50 to 1.63 mmol/L</td>
<td>&gt; 6.5 to 7.0 mg/dL, &gt; 1.63 to 1.75 mmol/L</td>
<td>&gt; 7.0 mg/dL, &gt; 1.75 mmol/L</td>
</tr>
<tr>
<td>CHEMISTRY</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>1.40 to &lt;LLN mg/dL</td>
<td>1.04 to 1.40 mg/dL</td>
<td>0.67 to 1.04 mg/dL</td>
<td>&lt; 0.67 mg/dL</td>
</tr>
<tr>
<td></td>
<td>1.2 to &lt;LLN mEq/L</td>
<td>0.9 to &lt; 1.2 mEq/L</td>
<td>0.6 to &lt; 0.9 mEq/L</td>
<td>&lt; 0.6 mEq/L</td>
</tr>
<tr>
<td></td>
<td>0.58 to &lt;LLN mmol/L</td>
<td>0.43 to &lt; 0.58 mmol/L</td>
<td>0.28 to &lt; 0.43 mmol/L</td>
<td>&lt; 0.28 mmol/L</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2.0 to &lt; LLN mg/dL</td>
<td>1.5 to &lt; 2.0 mg/dL</td>
<td>1.0 to &lt; 1.5 mg/dL</td>
<td>&lt; 1.0 mg/dL</td>
</tr>
<tr>
<td>Adult and Pediatric &gt; 14 Years</td>
<td>0.63 to &lt; LLN mmol/L</td>
<td>0.47 to &lt; 0.63 mmol/L</td>
<td>0.31 to &lt; 0.47 mmol/L</td>
<td>&lt; 0.31 mmol/L</td>
</tr>
<tr>
<td>Pediatric 1 Year–14 Years</td>
<td>3.0 to &lt;LLN mg/dL</td>
<td>2.5 to &lt; 3.0 mg/dL</td>
<td>1.5 to &lt; 2.5 mg/dL</td>
<td>&lt; 1.5 mg/dL</td>
</tr>
<tr>
<td></td>
<td>0.96 to &lt;LLN mmol/L</td>
<td>0.80 to &lt; 0.96 mmol/L</td>
<td>0.47 to &lt; 0.80 mmol/L</td>
<td>&lt; 0.47 mmol/L</td>
</tr>
<tr>
<td>Pediatric &lt; 1 Year</td>
<td>3.5 to &lt;LLN mg/dL</td>
<td>2.5 to &lt; 3.5 mg/dL</td>
<td>1.5 to &lt; 2.5 mg/dL</td>
<td>&lt; 1.5 mg/dL</td>
</tr>
<tr>
<td></td>
<td>1.12 to &lt;LLN mmol/L</td>
<td>0.80 to &lt; 1.12 mmol/L</td>
<td>0.47 to &lt; 0.80 mmol/L</td>
<td>&lt; 0.47 mmol/L</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>&gt; 1.0 to 1.5 × ULN</td>
<td>&gt; 1.5 to 2.5 × ULN</td>
<td>&gt; 2.5 to 5.0 × ULN</td>
<td>&gt; 5.0 × ULN</td>
</tr>
<tr>
<td>Adult and Pediatric &gt; 14 Days</td>
<td>NA</td>
<td>20.0 to 25.0 mg/dL</td>
<td>&gt; 25.0 to 30.0 mg/dL</td>
<td>&gt; 30.0 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>342 to 428 μmol/L</td>
<td>&gt; 428 to 513 μmol/L</td>
<td>&gt; 513 μmol/L</td>
</tr>
<tr>
<td>Infant, ≤ 14 Days (non-hemolytic)</td>
<td>NA</td>
<td>20.0 to 25.0 mg/dL</td>
<td>&gt; 25.0 to 30.0 mg/dL</td>
<td>&gt; 30.0 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>342 to 428 μmol/L</td>
<td>&gt; 428 to 513 μmol/L</td>
<td>&gt; 513 μmol/L</td>
</tr>
<tr>
<td>Infant, ≤ 14 Days (hemolytic)</td>
<td>NA</td>
<td>NA</td>
<td>20.0 to 25.0 mg/dL</td>
<td>&gt; 25.0 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>342 to 428 μmol/L</td>
<td>&gt; 428 μmol/L</td>
</tr>
<tr>
<td>Blood Urea Nitrogen</td>
<td>1.25 to 2.50 × ULN</td>
<td>&gt; 2.50 to 5.00 × ULN</td>
<td>&gt; 5.00 to 10.00 × ULN</td>
<td>&gt; 10.00 × ULN</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>&gt;ULN to 10.0 mg/dL</td>
<td>&gt; 10.0 to 12.0 mg/dL</td>
<td>&gt; 12.0 to 15.0 mg/dL</td>
<td>&gt; 15.0 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt;ULN to 597 μmol/L</td>
<td>&gt; 597 to 716 μmol/L</td>
<td>&gt; 716 to 895 μmol/L</td>
<td>&gt; 895 μmol/L</td>
</tr>
</tbody>
</table>
## CHEMISTRY

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypouricemia</strong></td>
<td>1.5 mg/dL to &lt; LLN</td>
<td>1.0 to &lt; 1.5 mg/dL</td>
<td>0.5 to &lt; 1.0 mg/dL</td>
<td>&lt; 0.5 mg/dL</td>
</tr>
<tr>
<td><strong>Adult and Pediatric</strong></td>
<td>87 μmol/L to &lt; LLN</td>
<td>57 to &lt; 87 μmol/L</td>
<td>27 to &lt; 57 μmol/L</td>
<td>&lt; 27 μmol/L</td>
</tr>
<tr>
<td></td>
<td><strong>Infant &lt; 1 Year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>1.0 mg/dl to &lt; LLN</td>
<td>0.5 to &lt; 1.0 mg/dL</td>
<td>&lt; 0.5 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>57 μmol/L to &lt; LLN</td>
<td>27 to &lt; 57 μmol/L</td>
<td>&lt; 27 μmol/L</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td>&gt; 1.50 to 2.00 mg/dL</td>
<td>&gt; 2.00 to 3.00 mg/dL</td>
<td>&gt; 3.00 to 6.00 mg/dL</td>
<td>&gt; 6.00 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt; 133 to 177 μmol/L</td>
<td>&gt; 177 to 265 μmol/L</td>
<td>&gt; 265 to 530 μmol/L</td>
<td>&gt; 530 μmol/L</td>
</tr>
<tr>
<td><strong>Bicarbonate</strong></td>
<td>16.0 mEq/L to &lt; LLN</td>
<td>11.0 to &lt; 16.0 mEq/L</td>
<td>8.0 to &lt; 11.0 mEq/L</td>
<td>&lt; 8.0 mEq/L</td>
</tr>
<tr>
<td><strong>Adult and Pediatric</strong></td>
<td>16.0 mmol/L to &lt; LLN</td>
<td>11.0 to &lt; 16.0 mmol/L</td>
<td>8.0 to &lt; 11.0 mmol/L</td>
<td>&lt; 8.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td><strong>Pediatric &lt; 4 Years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>11.0 mEq/L to &lt; LLN</td>
<td>8.0 to &lt; 11.0 mEq/L</td>
<td>&lt; 8.0 mEq/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.0 mmol/L to &lt; LLN</td>
<td>8.0 to &lt; 11.0 mmol/L</td>
<td>&lt; 8.0 mmol/L</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>NA</td>
<td>500 to 750 mg/dL</td>
<td>&gt; 750 to 1200 mg/dL</td>
<td>&gt; 1200 mg/dL</td>
</tr>
<tr>
<td>(Fasting)</td>
<td></td>
<td>5.64–8.47 mmol/L</td>
<td>&gt; 8.47–13.55 mmol/L</td>
<td>&gt; 13.55 mmol/L</td>
</tr>
<tr>
<td><strong>LDL (Fasting)</strong></td>
<td>130 to 160 mg/dL</td>
<td>&gt;160 to 190 mg/dL</td>
<td>&gt; 190 mg/dL</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Adult</strong></td>
<td>3.35 to 4.15 mmol/L</td>
<td>&gt;4.15 to 4.92 mmol/L</td>
<td>&gt; 4.92 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LDL (Fasting)</strong></td>
<td>110 to 130 mg/dL</td>
<td>&gt;130 to 190 mg/dL</td>
<td>&gt; 190 mg/dL</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Pediatric &gt;2 to &lt;18 years</strong></td>
<td>2.84 to 3.37 mmol/L</td>
<td>&gt;3.37 to 4.92 mmol/L</td>
<td>&gt; 4.92 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>
# CHEMISTRY

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia (Fasting)</td>
<td>200 to 239 mg/dL</td>
<td>&gt; 239 to 300 mg/dL</td>
<td>&gt; 300 mg/dL</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>5.16 to 6.19 mmol/L</td>
<td>&gt; 6.19 to 7.77 mmol/L</td>
<td>&gt; 7.77 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Pediatric &lt; 18 Years</td>
<td>170 to 199 mg/dL</td>
<td>&gt; 199 to 300 mg/dL</td>
<td>&gt; 300 mg/dL</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>4.39 to 5.15 mmol/L</td>
<td>&gt; 5.15 to 7.77 mmol/L</td>
<td>&gt; 7.77 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Creatine Kinase</td>
<td>3.0 to &lt; 6.0 × ULN</td>
<td>6.0 to &lt; 10.0 × ULN</td>
<td>10.0 to &lt; 20.0 × ULN</td>
<td>≥ 20.0 × ULN</td>
</tr>
</tbody>
</table>

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

# ENZYMES

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (SGOT)</td>
<td>1.25 to 2.50 × ULN</td>
<td>&gt; 2.50 to 5.00 × ULN</td>
<td>&gt; 5.00 to 10.00 × ULN</td>
<td>&gt; 10.00 × ULN</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>1.25 to 2.50 × ULN</td>
<td>&gt; 2.50 to 5.00 × ULN</td>
<td>&gt; 5.00 to 10.00 × ULN</td>
<td>&gt; 10.00 × ULN</td>
</tr>
<tr>
<td>GGT</td>
<td>1.25 to 2.50 × ULN</td>
<td>&gt; 2.50 to 5.00 × ULN</td>
<td>&gt; 5.00 to 10.00 × ULN</td>
<td>&gt; 10.00 × ULN</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>1.25 to 2.50 × ULN</td>
<td>&gt; 2.50 to 5.00 × ULN</td>
<td>&gt; 5.00 to 10.00 × ULN</td>
<td>&gt; 10.00 × ULN</td>
</tr>
<tr>
<td>Total Amylase</td>
<td>&gt; 1.0 to 1.5 × ULN</td>
<td>&gt; 1.5 to 2.0 × ULN</td>
<td>&gt; 2.0 to 5.0 × ULN</td>
<td>&gt; 5.0 × ULN</td>
</tr>
<tr>
<td>Pancreatic Amylase</td>
<td>&gt; 1.0 to 1.5 × ULN</td>
<td>&gt; 1.5 to 2.0 × ULN</td>
<td>&gt; 2.0 to 5.0 × ULN</td>
<td>&gt; 5.0 × ULN</td>
</tr>
<tr>
<td>Lipase</td>
<td>&gt; 1.0 to 1.5 × ULN</td>
<td>&gt; 1.5 to 3.0 × ULN</td>
<td>&gt; 3.0 to 5.0 × ULN</td>
<td>&gt; 5.0 × ULN</td>
</tr>
<tr>
<td>Albumin Pediatrics &lt;16 years</td>
<td>-</td>
<td>2.0 to &lt; LLN g/dL</td>
<td>&lt; 2.0 g/dL</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 to &lt; LLN g/L</td>
<td>&lt; 2 g/L</td>
<td></td>
</tr>
<tr>
<td>≥ 16 years</td>
<td>3.0 g/dL to &lt; LLN</td>
<td>2.0 to &lt; 3.0 g/dL</td>
<td>&lt; 2.0 g/dL</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>30 g/L to &lt; LLN</td>
<td>2.0 to &lt; 30 g/L</td>
<td>&lt; 20 g/L</td>
<td></td>
</tr>
<tr>
<td>URINALYSIS</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>Hematuria (Dipstick)</td>
<td>1+</td>
<td>2+</td>
<td>3-4+</td>
<td>NA</td>
</tr>
<tr>
<td>Hematuria (Quantitative) See Note below</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>&gt;ULN - 10 RBC/HPF</td>
<td>&gt; 10-75 RBC/HPF</td>
<td>&gt; 75 RBC/HPF</td>
<td>NA</td>
</tr>
<tr>
<td>Males</td>
<td>6-10 RBC/HPF</td>
<td>&gt; 10-75 RBC/HPF</td>
<td>&gt; 75 RBC/HPF</td>
<td>NA</td>
</tr>
<tr>
<td>Proteinuria (Dipstick)</td>
<td>1+</td>
<td>2-3+</td>
<td>4+</td>
<td>NA</td>
</tr>
<tr>
<td>Proteinuria, 24 Hour Collection Adult and Pediatric ≥ 10 Years</td>
<td>200 to 999 mg/24 h</td>
<td>&gt;999 to 1999 mg/24 h</td>
<td>&gt;1999 to 3500 mg/24 h</td>
<td>&gt; 3500 mg/24 h</td>
</tr>
<tr>
<td>Proteinuria, 24 Hour Collection Pediatric &gt; 3 Mo to &lt; 10 Years</td>
<td>201 to 499 mg/m²/24 h</td>
<td>&gt;499 to 799 mg/m²/24 h</td>
<td>&gt;799 to 1000 mg/m²/24 h</td>
<td>&gt; 1000 mg/ m²/24 h</td>
</tr>
<tr>
<td>Glycosuria (Dipstick)</td>
<td>1+</td>
<td>2-3+</td>
<td>4+</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchospasm (acute)</td>
<td>FEV1 or peak flow reduced to 70% to 80%</td>
<td>FEV1 or peak flow 50% to 69%</td>
<td>FEV1 or peak flow 25% to 49%</td>
</tr>
<tr>
<td>Dyspnea or Respiratory Distress</td>
<td>Dyspnea on exertion with no or minimal interference with usual social &amp; functional activities</td>
<td>Dyspnea on exertion causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Dyspnea at rest causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>Pediatric &lt; 14 Years</td>
<td>Wheezing OR minimal increase in respiratory rate for age</td>
<td>Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%</td>
<td>Dyspnea at rest causing inability to perform usual social &amp; functional activities OR Pulse oximetry &lt; 90%</td>
</tr>
</tbody>
</table>

### OCULAR/VISUAL

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uveitis</td>
<td>Asymptomatic but detectable on exam</td>
<td>Symptomatic anterior uveitis OR Medical intervention indicated</td>
<td>Posterior or pan-uveitis OR Operative intervention indicated</td>
</tr>
<tr>
<td>Visual Changes (from baseline)</td>
<td>Visual changes causing no or minimal interference with usual social &amp; functional activities</td>
<td>Visual changes causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Visual changes causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>SKIN</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Thinning detectable by study participant or caregiver (for disabled adults)</td>
<td>Thinning or patchy hair loss detectable by health care provider</td>
<td>Complete hair loss</td>
</tr>
<tr>
<td>Cutaneous Reaction – Rash</td>
<td>Localized macular rash</td>
<td>Diffuse macular, maculopapular, or morbilliform rash OR Target lesions</td>
<td>Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Slight or localized</td>
<td>Marked or generalized</td>
<td>NA</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>Slight or localized</td>
<td>Marked or generalized</td>
<td>NA</td>
</tr>
<tr>
<td>Pruritis (itching – no skin lesions)</td>
<td>(See also Injection Site Reactions: Pruritis associated with injection)</td>
<td>Itching causing no or minimal interference with usual social &amp; functional activities</td>
<td>Itching causing greater than minimal interference with usual social &amp; functional activities</td>
</tr>
</tbody>
</table>
# Gastrointestinal

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>Loss of appetite without decreased oral intake</td>
<td>Loss of appetite associated with decreased oral intake without significant weight loss</td>
<td>Loss of appetite associated with significant weight loss</td>
</tr>
<tr>
<td>Ascites</td>
<td>Asymptomatic</td>
<td>Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)</td>
<td>Symptomatic despite intervention</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>NA</td>
<td>Symptomatic AND Medical intervention indicated</td>
<td>Radiologic, endoscopic, or operative intervention indicated</td>
</tr>
<tr>
<td>Constipation</td>
<td>NA</td>
<td>Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas</td>
<td>Obstipation with manual evacuation indicated</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr</td>
<td>Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.</td>
<td>Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated</td>
</tr>
<tr>
<td>Pediatric &lt; 1 Year</td>
<td>Liquid stools (more unformed than usual) but usual number of stools</td>
<td>Liquid stools with increased number of stools OR Mild dehydration</td>
<td>Liquid stools with moderate dehydration</td>
</tr>
<tr>
<td>Dysphagia-Odynophagia</td>
<td>Symptomatic but able to eat usual diet</td>
<td>Symptoms causing altered dietary intake without medical intervention indicated</td>
<td>Symptoms causing severely altered dietary intake with medical intervention indicated</td>
</tr>
<tr>
<td>Condition (clinical exam)</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td>Mucositis/Stomatitis</td>
<td>Erythema of the mucosa</td>
<td>Patchy pseudomembranes or ulcerations</td>
<td>Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma</td>
</tr>
<tr>
<td>Proctitis, Dysphagia-Odynophagia</td>
<td>See also Mucositis/Stomatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Transient (&lt; 24 hours) or intermittent nausea with no or minimal interference with oral intake</td>
<td>Persistent nausea resulting in decreased oral intake for 24–48 hours</td>
<td>Persistent nausea resulting in minimal oral intake for &gt; 48 hours OR Aggressive rehydration indicated (eg, IV fluids)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>NA</td>
<td>Symptomatic AND Hospitalization not indicated (other than ER visit)</td>
<td>Symptomatic AND Hospitalization indicated (other than ER visit)</td>
</tr>
<tr>
<td>Proctitis (functional-symptomatic)</td>
<td>Rectal discomfort AND No intervention indicated</td>
<td>Symptoms causing greater than minimal interference with usual social &amp; functional activities OR Medical intervention indicated</td>
<td>Symptoms causing inability to perform usual social/functional activities OR Operative intervention indicated</td>
</tr>
<tr>
<td>Also see Mucositis/ Stomatitis for Clinical Exam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Transient or intermittent vomiting with no or minimal interference with oral intake</td>
<td>Frequent episodes of vomiting with no or mild dehydration</td>
<td>Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated</td>
</tr>
<tr>
<td>NEUROLOGICAL</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)</td>
<td>Alteration causing no or minimal interference with usual social &amp; functional activities</td>
<td>Alteration causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Alteration causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)</td>
<td>Changes causing no or minimal interference with usual social &amp; functional activities</td>
<td>Mild lethargy or somnolence causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social &amp; functional activities</td>
<td>Symptomatic ataxia causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Symptomatic ataxia causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)</td>
<td>Disability causing no or minimal interference with usual social &amp; functional activities OR Specialized resources not indicated</td>
<td>Disability causing greater than minimal interference with usual social &amp; functional activities OR Specialized resources on part-time basis indicated</td>
<td>Disability causing inability to perform usual social &amp; functional activities OR Specialized resources on a full-time basis indicated</td>
</tr>
<tr>
<td>CNS Ischemia (acute)</td>
<td>NA</td>
<td>NA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>Developmental delay – Pediatric ≤ 16 Years</td>
<td>Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</td>
<td>Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</td>
<td>Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</td>
</tr>
<tr>
<td>NEUROLOGICAL</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Headache</td>
<td>Symptoms causing no or minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>Insomnia</td>
<td>NA</td>
<td>Difficulty sleeping causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Difficulty sleeping causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>Neuromuscular Weakness (including myopathy &amp; neuropathy)</td>
<td>Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social &amp; functional activities</td>
<td>Muscle weakness causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Muscle weakness causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>Neurosensory Alteration (including paresthesia and painful neuropathy)</td>
<td>Asymptomatic with sensory alteration on exam OR minimal paresthesia causing no or minimal interference with usual social &amp; functional activities</td>
<td>Sensory alteration or paresthesia causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Sensory alteration or paresthesia causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>Seizure: (new onset)</td>
<td>NA</td>
<td>1 seizure</td>
<td>2–4 seizures</td>
</tr>
</tbody>
</table>
### NEUROLOGICAL

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure: (pre-existing)</td>
<td>NA</td>
<td>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</td>
<td>Change in seizure character from baseline either in duration or quality (eg, severity or focality)</td>
<td>Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)</td>
</tr>
<tr>
<td>For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure – Pediatric &lt; 18 Years</td>
<td>Seizure, generalized onset with or without secondary generalization, lasting &lt; 5 minutes with &lt; 24 hours post ictal state</td>
<td>Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with &lt; 24 hours post ictal state</td>
<td>Seizure, generalized onset with or without secondary generalization, lasting &gt; 20 minutes</td>
<td>Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation</td>
</tr>
<tr>
<td>Syncope (not associated with a procedure)</td>
<td>NA</td>
<td>Present</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Vertigo causing no or minimal interference with usual social &amp; functional activities</td>
<td>Vertigo causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Vertigo causing inability to perform usual social &amp; functional activities</td>
<td>Disabling vertigo causing inability to perform basic self-care functions</td>
</tr>
</tbody>
</table>
## MUSCULOSKELETAL

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>Joint pain causing no or minimal interference with usual social &amp; functional activities</td>
<td>Joint pain causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Joint pain causing inability to perform usual social &amp; functional activities</td>
<td>Disabling joint pain causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Stiffness or joint swelling causing no or minimal interference with usual social &amp; functional activities</td>
<td>Stiffness or joint swelling causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Stiffness or joint swelling causing inability to perform usual social &amp; functional activities</td>
<td>Disabling joint stiffness or swelling causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Bone Mineral Loss</td>
<td>BMD t-score or z-score $\leq -2.5$ to $-1.0$</td>
<td>BMD t-score or z-score $&lt; -2.5$</td>
<td>Pathological fracture (including loss of vertebral height)</td>
<td>Pathologic fracture causing life-threatening consequences</td>
</tr>
<tr>
<td>Pediatric $&lt; 21$ Years</td>
<td>BMD z-score $-2.5$ to $-1.0$</td>
<td>BMD z-score $&lt; -2.5$</td>
<td>Pathological fracture (including loss of vertebral height)</td>
<td>Pathologic fracture causing life-threatening consequences</td>
</tr>
<tr>
<td>Myalgia (non-injection site)</td>
<td>Muscle pain causing no or minimal interference with usual social &amp; functional activities</td>
<td>Muscle pain causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Muscle pain causing inability to perform usual social &amp; functional activities</td>
<td>Disabling muscle pain causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>NA</td>
<td>Asymptomatic with radiographic findings AND No operative intervention indicated</td>
<td>Symptomatic bone pain with radiographic findings OR Operative intervention indicated</td>
<td>Disabling bone pain with radiographic findings causing inability to perform basic self-care functions</td>
</tr>
</tbody>
</table>
## SYSTEMIC

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

**Note:** Standardized severity grading continues to evaluate grade 5 (death) as per the amended criteria for severe systemic events.
## INJECTION SITE REACTION

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site Pain (pain</td>
<td>Pain/tenderness causing no or minimal limitation of use of limb</td>
<td>Pain/tenderness limiting use of limb OR Pain/tenderness causing greater</td>
<td>Pain/tenderness causing inability to perform usual social &amp; functional</td>
<td>Pain/tenderness causing inability to perform basic self-care function</td>
</tr>
<tr>
<td>without touching) Or</td>
<td></td>
<td>than minimal interference with usual social &amp; functional activities</td>
<td>activities OR Hospitalization (other than ER visit) indicated for</td>
<td>(other than ER visit) indicated for management of pain/tenderness</td>
</tr>
<tr>
<td>Tenderness (pain when area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>is touched)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td>Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm²)</td>
<td>Erythema OR Induration OR Edema &gt; 9 cm any diameter (or &gt; 81 cm²)</td>
<td>Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR</td>
<td>Necrosis (involving dermis and deeper tissue)</td>
</tr>
<tr>
<td>(Localized), &gt; 15 Years</td>
<td>Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter</td>
<td>Erythema OR Induration OR Edema &gt; 2.5 cm diameter but &lt; 50% surface</td>
<td>Drainage</td>
<td></td>
</tr>
<tr>
<td>Pediatric ≤ 15 Years</td>
<td></td>
<td>area of the extremity segment (eg, upper arm/thigh)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritis Associated with</td>
<td>Itching localized to injection site AND Relived spontaneously or with</td>
<td>Itching beyond the injection site but not generalized OR Itching</td>
<td>Generalized itching causing inability to perform usual social &amp;</td>
<td>NA</td>
</tr>
<tr>
<td>Injection</td>
<td>&lt; 48 h treatment</td>
<td>localized to injection site requiring ≥ 48 h treatment</td>
<td>functional activities</td>
<td></td>
</tr>
<tr>
<td>See also Skin: Pruritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(itching—no skin lesions)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## ENDOCRINE/METABOLIC

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

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

## INFECTION

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

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

**Usual Social & Functional Activities:** Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.
Appendix 5. Definitions of Stage 3 Opportunistic Illnesses in HIV (CDC Guidelines)

1. Candidiasis of bronchi, trachea, or lungs
2. Candidiasis of esophagus
3. Cervical cancer, invasive
4. Coccidioidomycosis, disseminated or extrapulmonary
5. Cryptococcosis, extrapulmonary
6. Cryptosporidiosis, chronic intestinal (> 1 month duration)
7. Cytomegalovirus disease (other than liver, spleen or nodes)
8. Cytomegalovirus retinitis (with loss of vision)
9. Encephalopathy, HIV-related
10. Herpes simplex: chronic ulcer(s) (> 1 month duration); or bronchitis, pneumonitis or esophagitis
11. Histoplasmosis, disseminated or extrapulmonary
12. Isosporiasis, chronic intestinal (> 1 month duration)
13. Kaposi’s sarcoma
14. Lymphoma, Burkitt’s (or equivalent term)
15. Lymphoma, immunoblastic (or equivalent term)
16. Lymphoma, primary, of brain
17. Mycobacterium avium complex or 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 {Selik et al 2014}
Appendix 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

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

Women are considered to be in a postmenopausal state when they are $\geq 54$ 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 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 even true for women of childbearing potential with infrequent or irregular periods. Female subjects must agree to one of the following from Screening until 30 days following the end of relevant systemic exposure.
• Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject’s preferred and usual lifestyle.

Or

• Consistent and correct use of 1 of the following methods of birth control listed below.
  — Intrauterine device (IUD) with a failure rate of <1% per year
  — 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. **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.